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(54) Title: INHIBITORS OF FARNESYL–PROTEIN TRANSFERASE

(57) Abstract

The present invention is directed to compounds which inhibit farnesyl–protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl–protein transferase and the farnesylation of the oncogene protein Ras.

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem. 62*:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem. 61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesyl-

ation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al., Science, 260*:1934-1937 (1993) and G.L. James *et al., Science, 260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al., Proc. Natl. Acad. Sci U.S.A., 91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al., Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al., ibid*; Casey *et al., ibid*; Schafer *et al., Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al., Cell, 62*:81-88 (1990); Schaber *et al., J. Biol. Chem., 265*:14701-14704 (1990); Schafer *et al., Science, 249*:1133-1139 (1990); Manne *et al., Proc. Natl. Acad. Sci USA, 87*:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor

of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in four general classes (S. Graham, *Expert Opinion Ther. Patents,* (1995) 5:1269-1285). The first are analogs of farnesyl diphosphate (FPP), while a second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. Bisubstrate inhibitors and inhibitors of farnesyl-protein transferase that are non-competitive with the substrates have also been described. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al., ibid*; Reiss *et. al., ibid*; Reiss *et al., PNAS, 88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al., Science, 260*:1934-1937 (1993); Graham, et al., *J. Med. Chem., 37*, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

Recently, certain tricyclic compounds which optionally incorporate a piperidine moiety have been disclosed to be inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing compounds which are claimed to be inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1). WO 95/09001 discloses imidazolyl containing compounds that are inhibitors of farnesyl protein transferase.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

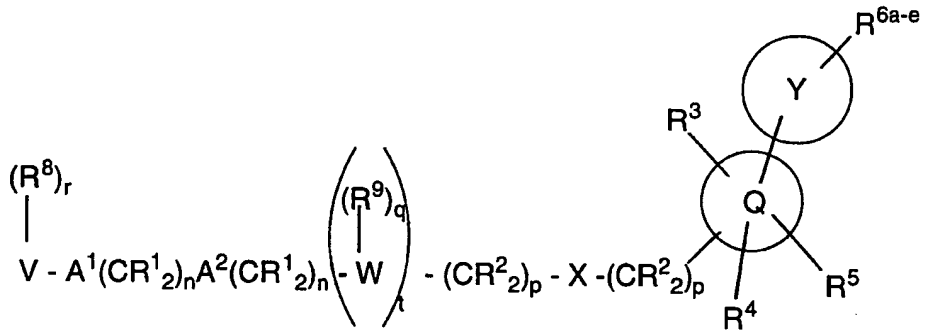
It is, therefore, an object of this invention to develop

low molecular weight compounds that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

SUMMARY OF THE INVENTION

The present invention comprises bicyclic compounds which inhibit the farnesyl-protein transferase. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the formula A:



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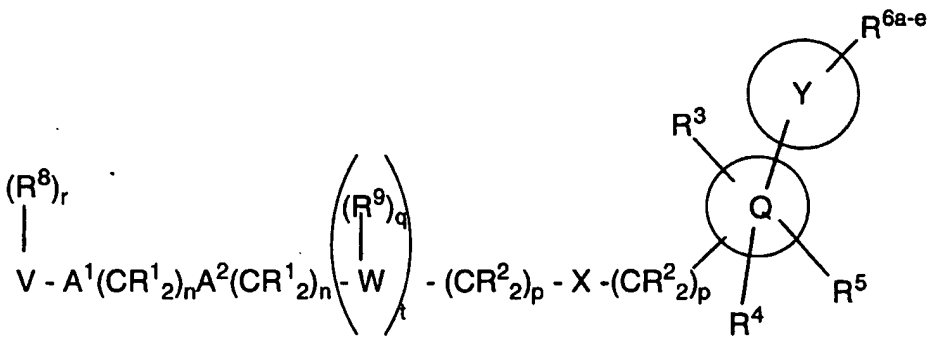
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



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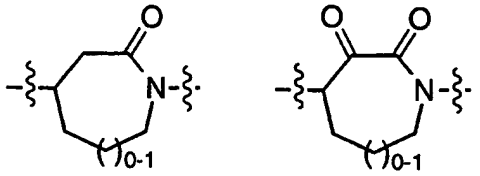
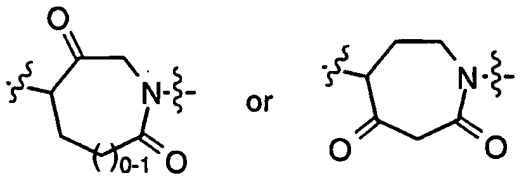
wherein:

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not





Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

R^1 and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

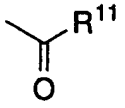
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^7 is selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c)  ,

d) $-SO_2R^{11}$,

e) $N(R^{10})_2$ or

f) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is independently selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)2-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

R^{13} is selected from hydrogen, C_1-C_6 alkyl, cyano, C_1-C_6 alkylsulfonyl and C_1-C_6 acyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, or S(O)$_m$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

W is a heterocycle;

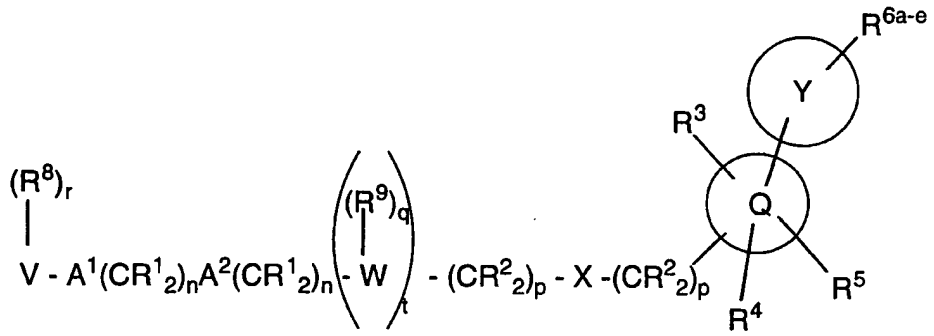
X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR^7-, -NR^7C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^7C(O)-, -NR^7-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$- or -S(=O)$_m$-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is independently 0, 1, 2, 3 or 4;
q is 0, 1, 2 or 3;
r is 0 to 5, provided that r is 0 when V is hydrogen; and

t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the compounds of this invention is illustrated by the following formula A:



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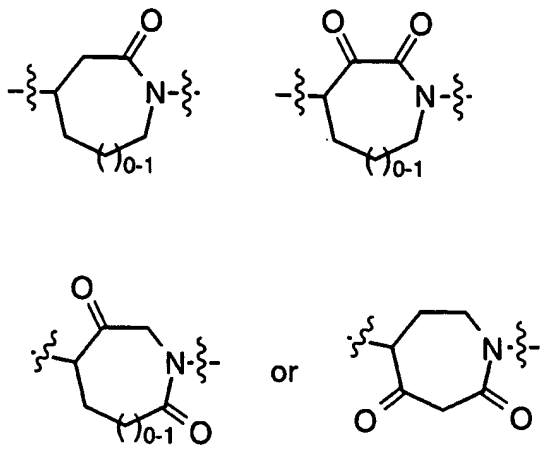
wherein:

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR13)- or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not



Y is selected from: phenyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thiazolyl, isothiazolyl, tetrahydrofuryl, piperdinyl, thiazolidinyl, piperazinyl and tetrahydrothienyl;

R^1 is independently selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl;

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl;

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

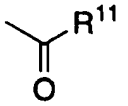
any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-,

-CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^7 is selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c)  ,

d) $-SO_2R^{11}$,

e) $N(R^{10})_2$ or

f) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)$_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

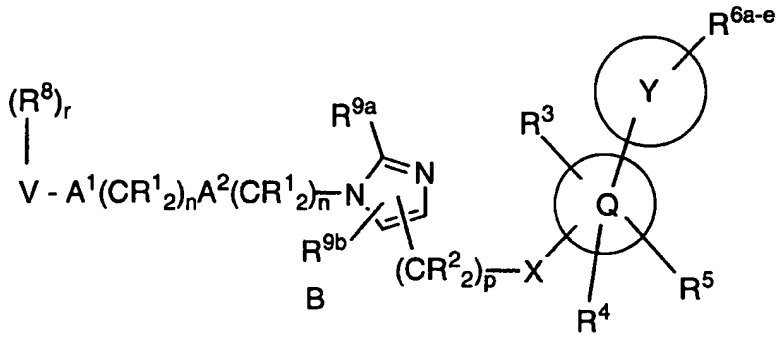
W is a heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, triazolyl or isoquinolinyl;

X is a bond, O, -C(=O)-, -CH=CH-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$ or $-S(=O)_m-$;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is independently 0, 1, 2, 3 or 4;
q is 0, 1, 2 or 3;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

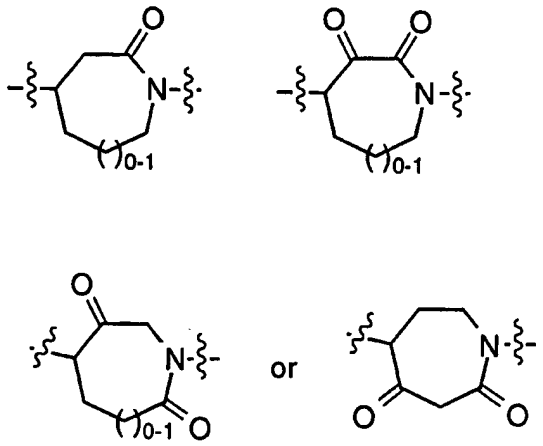
A preferred embodiment of the compounds of this invention are illustrated by the formula B:



wherein:

Q is a 5 or 6 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2

additional heteroatoms selected from N, S and O, and which also comprises a carbonyl or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not



Y is selected from: phenyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thiazolyl, isothiazolyl, tetrahydrofuryl, piperdinyl, thiazolidinyl, piperazinyl and tetrahydrothiophenyl;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl and halogen;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)$_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

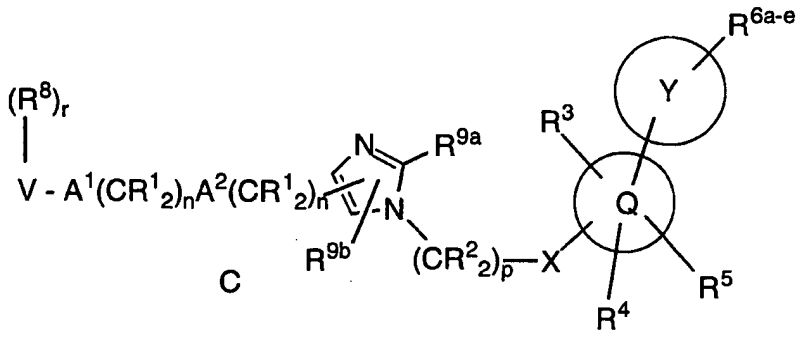
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

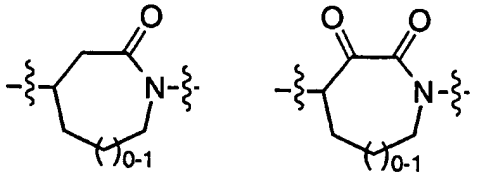
or a pharmaceutically acceptable salt thereof.

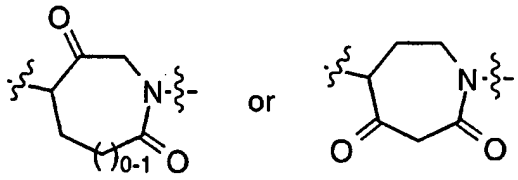
Another preferred embodiment of the compounds of this invention are illustrated by the formula C:



wherein:

Q is a 5 or 6 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not





Y is selected from: phenyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thiazolyl, isothiazolyl, tetrahydrofuryl, piperdinyl, thiazolidinyl, piperazinyl and tetrahydrothiophenyl;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-,

$R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-C(NR^{10})-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-C(NR^{10})-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl and halogen;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-

C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)$_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

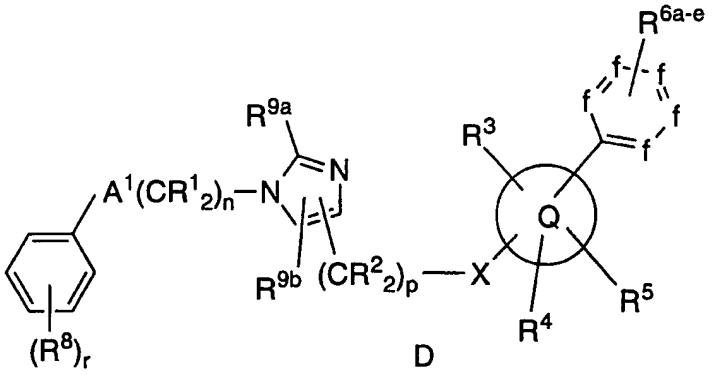
X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;
and
r is 0 to 5, provided that r is 0 when V is hydrogen;

or a pharmaceutically acceptable salt thereof.

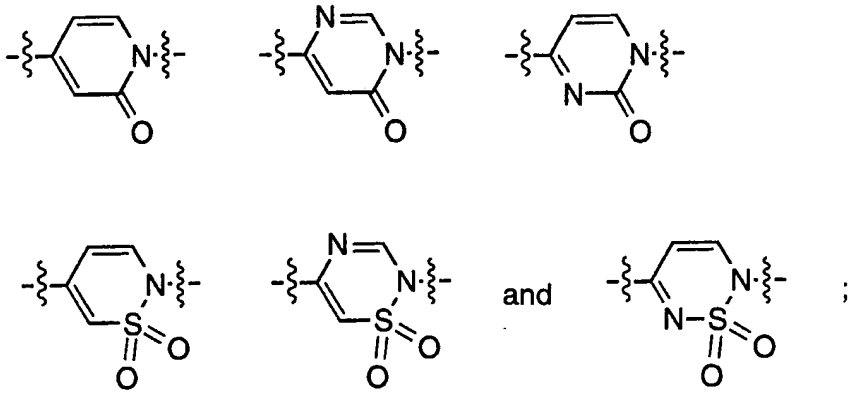
In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D:



D

wherein:

Q is selected from



;

from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-

C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)$_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

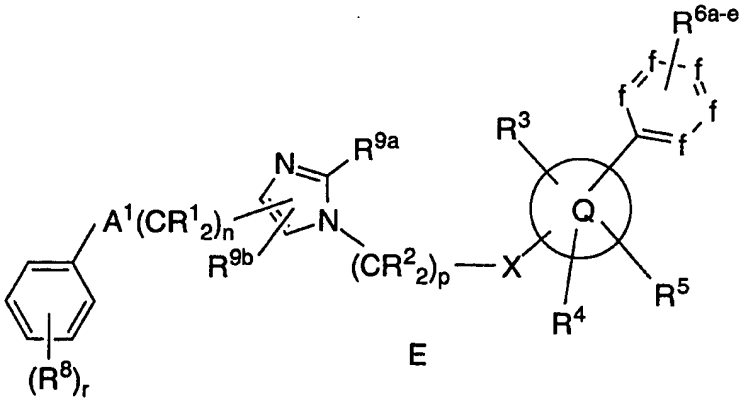
A^1 is selected from: a bond, -C(O)-, O, -N(R^{10})-, or S(O)$_m$;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-,

n is 0 or 1; provided that n is not 0 if A^1 is a bond, O, -N(R^{10})- or S(O)$_m$;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4; and
r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

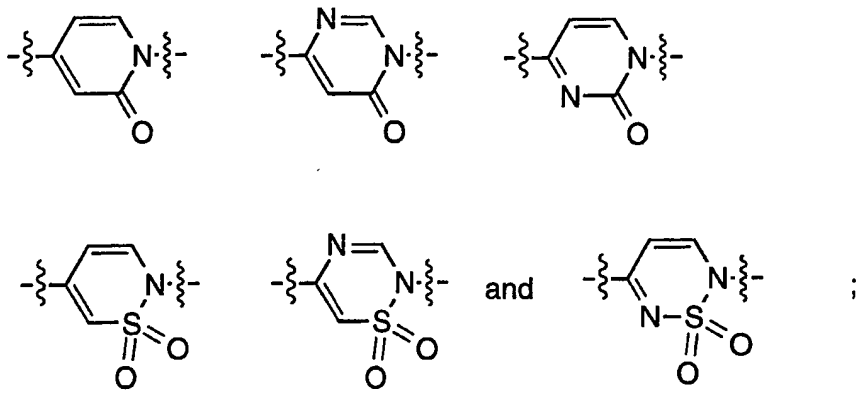
In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula E:



E

wherein:

Q is selected from



from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)2-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

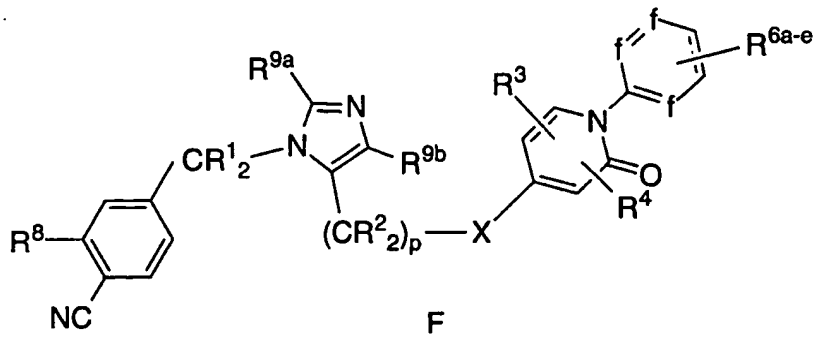
R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

n is 0 or 1;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;
and
r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula F:



F

wherein:

from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or F,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, CH_3 and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-,

$R^{10}{}_2N$-C(NR^{10})-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-C(NR^{10})-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)$_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

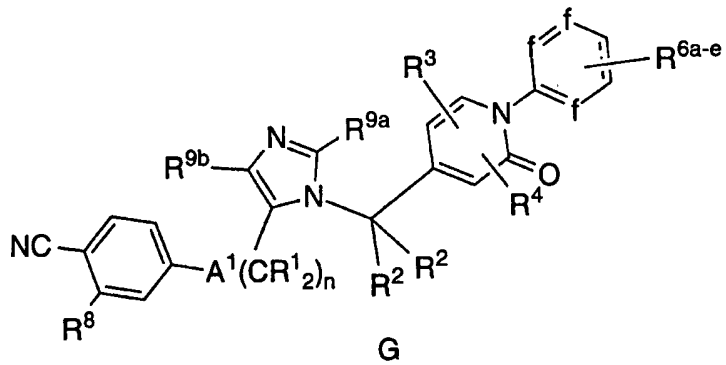
R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula G:



G

wherein:

from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,
b) aryl, heterocycle or C_3-C_{10} cycloalkyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, CH_3 and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)4$- and -$(CH_2)3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, $(C_1$-C_6 alkyl$)_2$-amino-C_1-C_6 alkyl,

acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^{10})-, or S(O)$_m$;

m is 0, 1 or 2; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

The preferred compounds of the instant invention are selected from:

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-[3-(2-Oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(6'-Methyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}-2-methoxy-benzonitrile

4-[3-(2-Oxo-1-pyrimidin-2-yl-1,2-dihydro-pyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-{3-[1-(6-chloro-pyrazin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile

4-[3-(3'-Methyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(6'-chloro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(6-'Triflouromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-{3-[1-(6-Chloro-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile

4-{3-[1-(6-Chloro-pyrazin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-2-methoxy-benzonitrile

4-{3-[1-(6-Chloro-4-methyl-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile

3-[3-(6'-chloro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(5'-Cyano-2-oxo-2H-[1,3']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(4'-Trifluoromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(6'-Methoxy-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(3'-Nitro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(3'-Trifluoromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-{3-[1-(6-Trifluromethyl-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-yl methyl]-3H-imidazol-4-ylmethyl}-benzonitrile

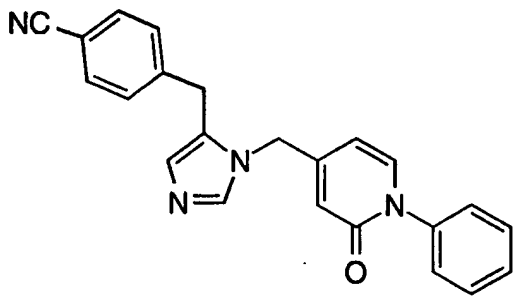
4-[5-(4-Bromophenoxy)imidazol-1-ylmethyl]-1-(6-cyanopyrazin-2-yl)-1H-pyridin-2-one

4-{5-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-imidazol-1-ylmethyl}-2-methoxy-benzonitrile

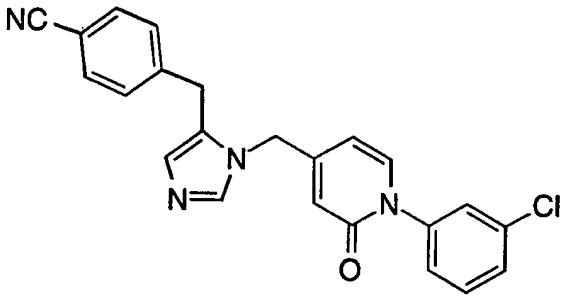
or the pharmaceutically acceptable salts thereof.

Specific examples of the compounds of the invention are:

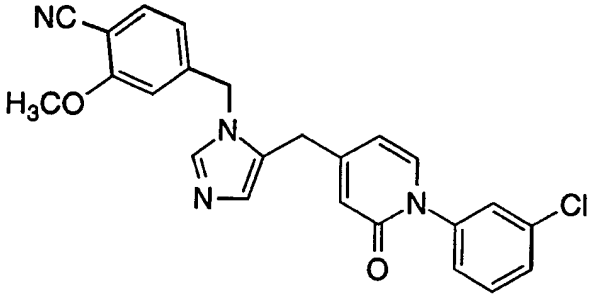
4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile



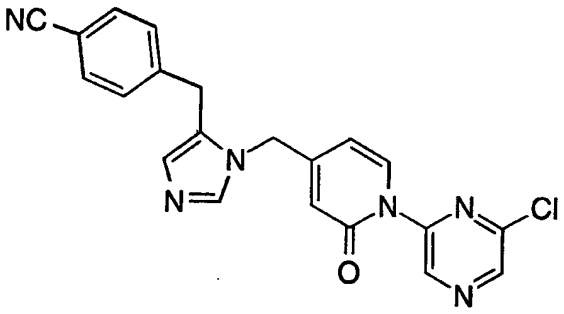
4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile



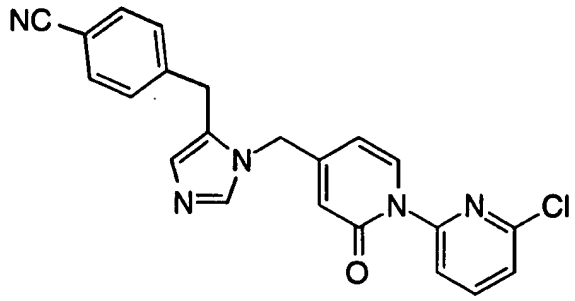
4-{5-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-imidazol-1-ylmethyl}-2-methoxy-benzonitrile



4-{3-[1-(6-Chloro-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile



3-[3-(6'-chloro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile



or the pharmaceutically acceptable salts thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^1, R^2 etc.) occurs more than one time in any constituent, its definition on each occurence is independent at every other occurence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" and the alkyl portion of aralkyl and similar terms, is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

As used herein, "cycloalkyl" is intended to include non-aromatic cyclic hydrocarbon groups having the specified number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

"Alkenyl" groups include those groups having the specified number of carbon atoms and having one or several double bonds. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like.

"Alkynyl" groups include those groups having the specified number of carbon atoms and having one triple bonds. Examples of

alkynyl groups include acetylene, 2-butynyl, 2-pentynyl, 3-pentynyl and the like.

"Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl," and the aryl portion of aroyl and aralkyl, is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

As used herein in the definition of R^3, R^4, R^5 and R^{6a-e}, the term "the substituted group" is intended to mean a substituted C_{1-8} alkyl, substituted C_{2-8} alkenyl, substituted C_{2-8} alkynyl, substituted aryl or substituted heterocycle from which the substituent(s) R^3, R^4, R^5 and R^{6a-e} are selected.

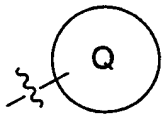
As used herein in the definition of R^7, the substituted C_{1-8} alkyl, substituted C_{3-6} cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroaryl-sulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound.

As used herein, when no specific substituents are set forth, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted on a substitutable ring carbon atom with 1 or 2 substitutents selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6$ alkyl$)_2$, NO_2, CN, (C_1-C_6 alkyl)O-, -OH, (C_1-C_6 alkyl)$S(O)_m$-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)-, N_3,(C_1-C_6 alkyl)OC(O)NH-,

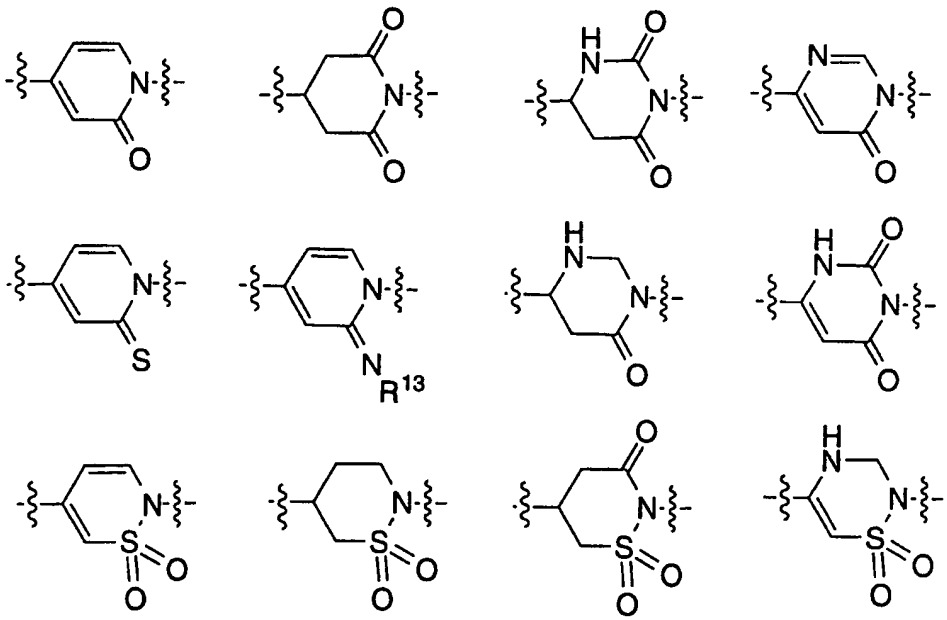
phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C_1-C_{20} alkyl.

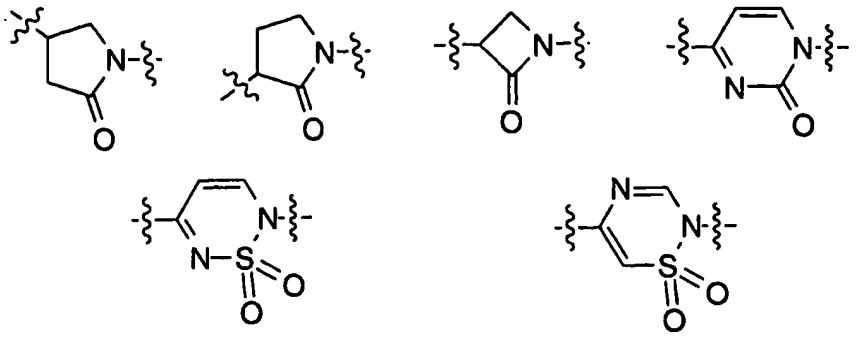
Lines drawn into the ring systems from substituents (such as from R^3, R^4, Q etc.) means that the indicated bond may be attached to any of the substitutable ring carbon or nitrogen atoms.

The substituent illustrated by the structure

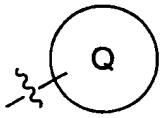


represents a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y and includes the following ring systems:

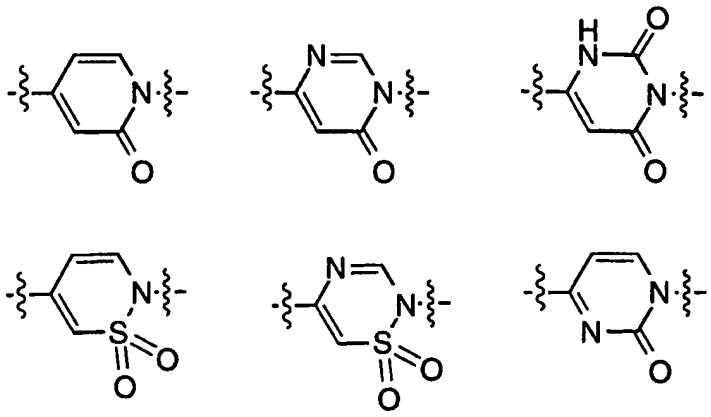


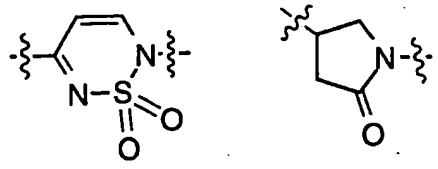


Preferably, the structure

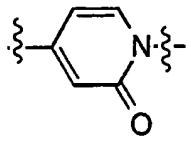


is selected from:



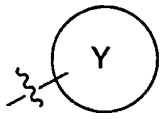


Most preferably, Q is

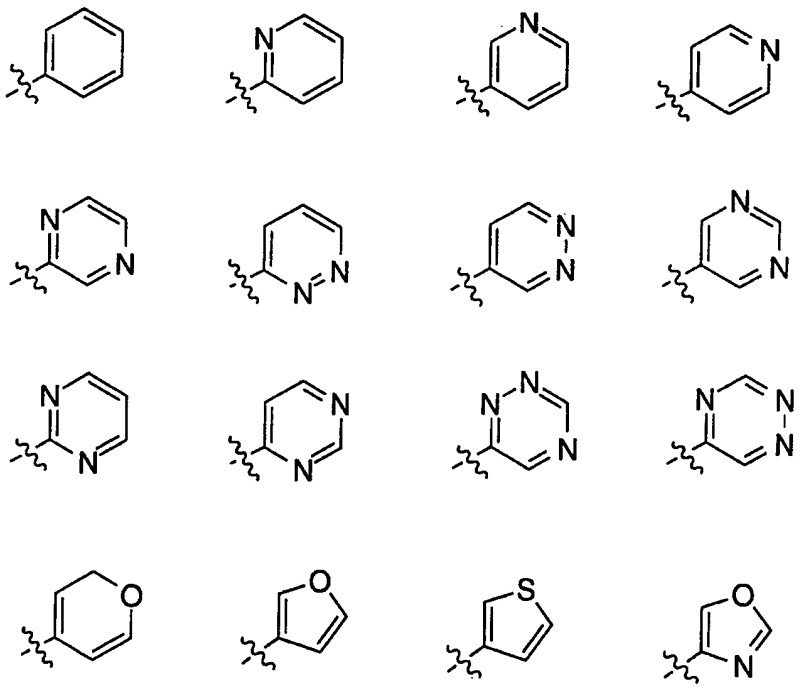


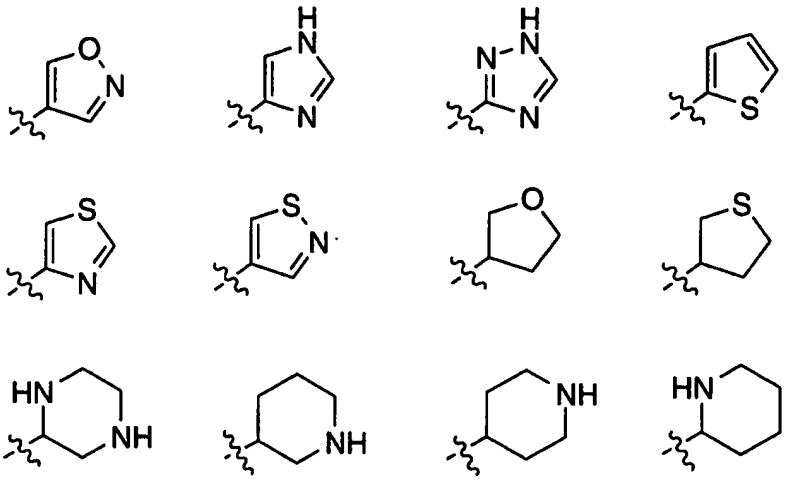
It is understood that such rings may be substituted by R^3, R^4 and/or R^5 as defined hereinabove.

The substituent illustrated by the structure

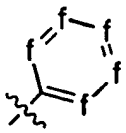


represents a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom and includes the following ring systems:

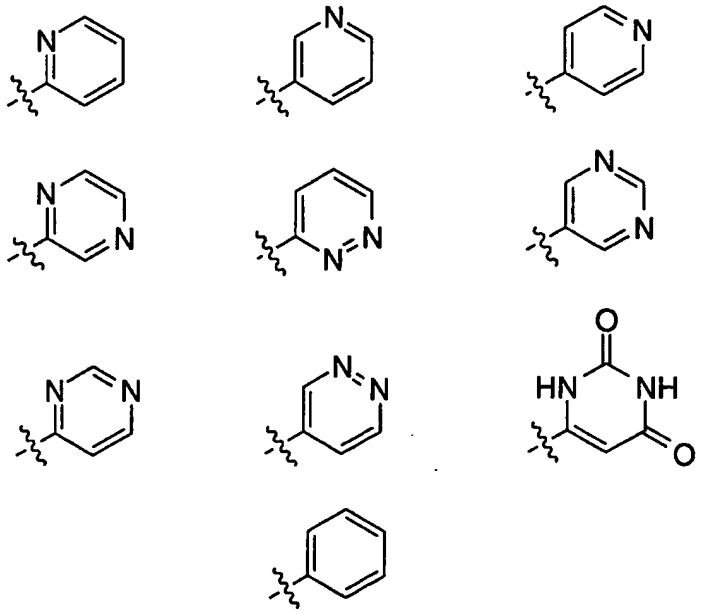




Preferably Y is the moiety designated by the following structure

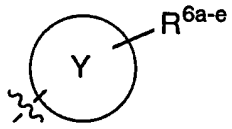


which represents an aromatic 6-membered ring and includes the following ring systems:

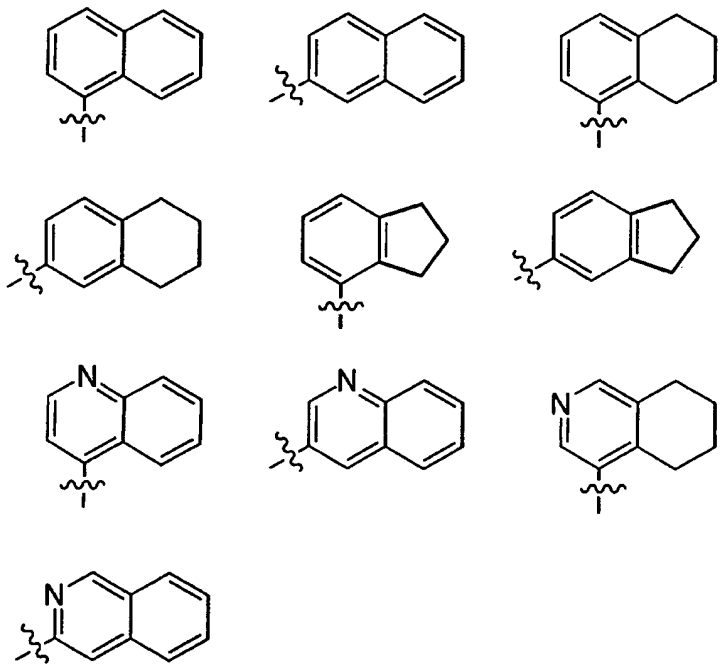


wherein it is understood that one of the ring carbon atoms is substituted with Q. Preferably, the Y is selected from phenyl and pyridyl.

The moiety described as



where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH-, $-(CH_2)_4-$ and $-(CH_2)_4-$ includes, but is not limited to, the following structures:



It is understood that such fused ring moieties may be further substituted by the remaining R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

Preferably, R^1 and R^2 are independently selected from: hydrogen, $R^{11}C(O)O-$, $-N(R^{10})_2$, $R^{10}C(O)NR^{10}-$, $R^{10}O-$ or unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the

substituted C_1-C_6 alkyl is selected from unsubstituted or substituted phenyl, -$N(R^{10})_2$, $R^{10}O$- and $R^{10}C(O)NR^{10}$-.

Preferably, R^3 is selected from:

a) hydrogen,

b) C_3-C_{10} cycloalkyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, CN, NO_2, $R^{10}C(O)$- or -$N(R^{10})_2$,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-.

Preferably, R^4 is selected from: hydrogen, halogen, trifluoromethyl, trifluoromethoxy and C_1-C_6 alkyl.

Preferably, R^5 is hydrogen.

Preferably, R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) C_3-C_{10} cycloalkyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, CN, NO_2, $R^{10}C(O)$- or -$N(R^{10})_2$,

c) unsubstituted C_1-C_6 alkyl; and

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, C_3-C_{10} cycloalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)$- or -$N(R^{10})_2$.

Preferably, R^8 is independently selected from:

a) hydrogen, and

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 perfluoroalkyl, $R^{10}O$- or CN.

Preferably, R^9 is hydrogen, halogen or methyl.

Preferably, R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl, aryl and substituted aryl. More preferably, R^{10} is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, A^1 and A^2 are independently selected from: a bond, $-C(O)NR^{10}-$, $-NR^{10}C(O)-$, O, $-N(R^{10})-$, $-S(O)_2N(R^{10})-$ and $-N(R^{10})S(O)_2-$.

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl and pyridyl.

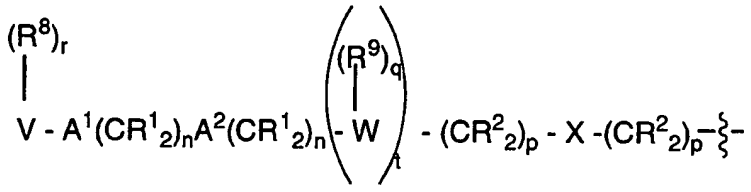
Preferably, W is selected from imidazolinyl, imidazolyl, oxazolyl, pyrazolyl, pyyrolidinyl, thiazolyl and pyridyl. More preferably, W is selected from imidazolyl and pyridyl.

Preferably, n and r are independently 0, 1, or 2.

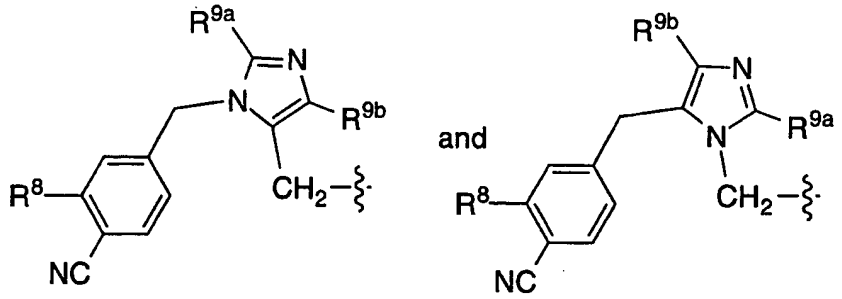
Preferably s is 0.

Preferably t is 1.

Preferably, the moiety



is selected from:



It is intended that the definition of any substituent or variable (e.g., R^1, R^2, R^9, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus,

-$N(R^{10})_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-17, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^3, R^6 and R^8, as shown in the Schemes, represent the substituents R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e} and R^8; although only one such R^3, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the

reactions shown are also applicable when such aryl or heterocyclic moieties contain multiple substituents.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein.

Synopsis of Schemes 1-17:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. Schemes 1-8 illustrate synthesis of the instant bicyclic compounds which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 1, for example, a bicyclic intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridinonyl alcohol **2** may be synthesized starting from the corresponding isonicotinate **1** according to procedures described by Boekelhiede and Lehn (*J. Org. Chem.*, 26:428-430 (1961)). The alcohol is then protected and reacted under Ullmann coupling conditions with a suitably substituted phenyl iodide, to provide the intermediate bicyclic alcohol **3**. The intermediate alcohol **3** may converted to the corresponding bromide **4**. The bromide **4** may be coupled to a suitably substituted benzylimidazolyl **5** to provide, after deprotection, the instant compound **6**.

Schemes 2-4 illustrate methods of synthesizing related or alcohol intermediates, which can then be processed as described in Scheme 1. Thus, Scheme 2 illustrates preparation of a pyridyl-pyridinonyl alcohol and thienylpyridinonyl alcohol starting with the suitably substituted halogenated heterocycles.

Scheme 3 illustrates preparation of the intermediate bromide **9** wherein the preferred pyridinone is replced by a saturated lactam. Acylation of a suitably substituted aniline **7** with a suitably substituted brominated acyl chloride provides the acylated intermediate **8**. Closure of the lactam ring provides the intermediate alcohol, which is converted to the bromide as described above.

Scheme 4 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **10** may be selectively iodinated to provide the 5-iodoimidazole **11**. That imidazole **11** may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **12**. Intermediate **12** can then undergo the alkylation reactions that were described hereinabove.

Scheme 5 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-amino-alkylimidazole **13**, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine **14**. The amine **14** may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

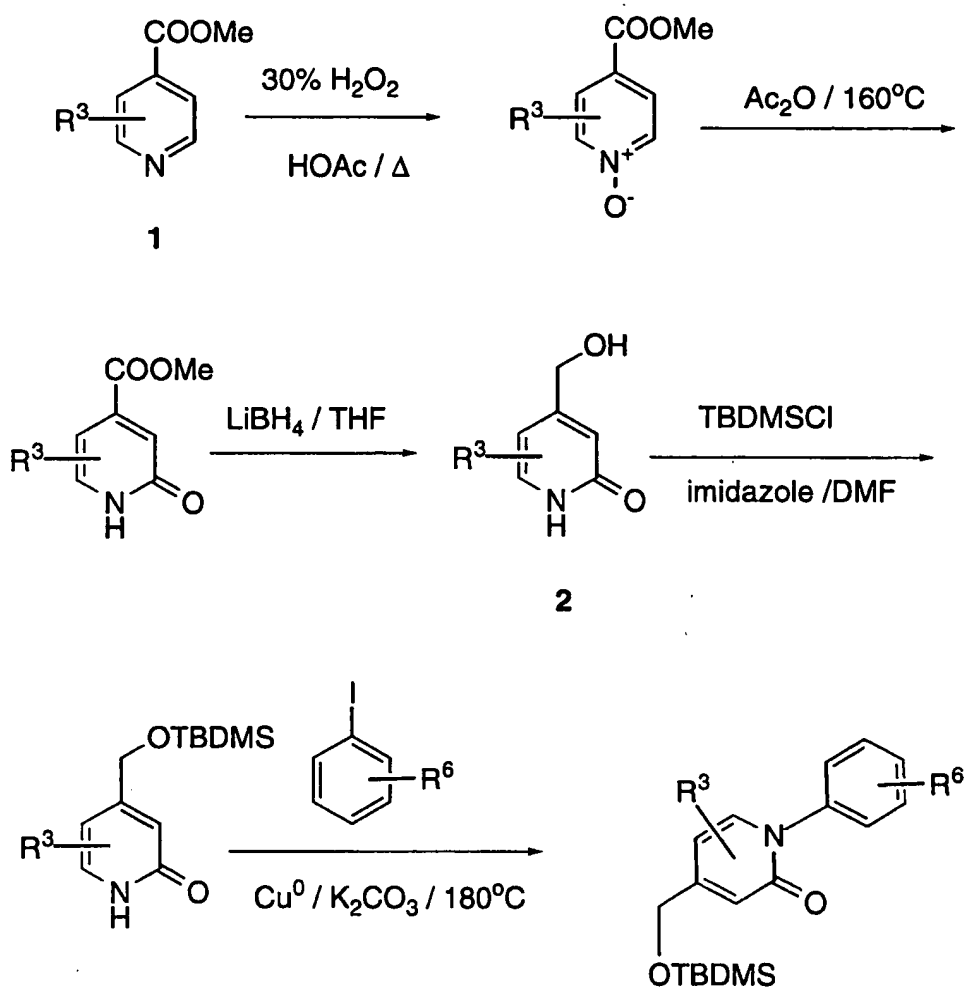
Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 6. The suitably substituted phenol **15** may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole **16**. After selective protection of one of the imidazolyl nitrogens, the intermediate **17** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 7. Thus, the

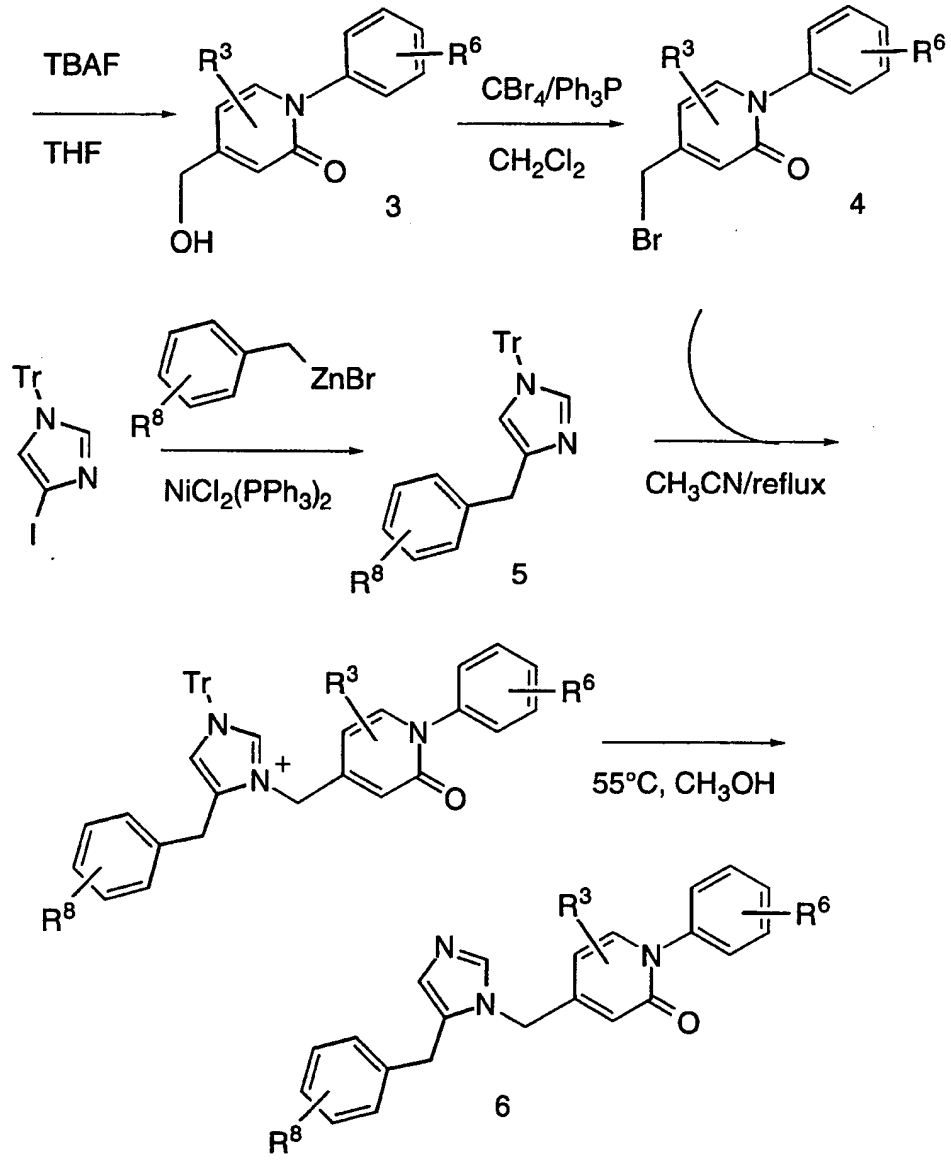
N-protected imidazolyl iodide **18** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **19**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 1) provides the instant compound **20**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 8 illustrates incorporation of an acetyl moiety as the $(CR^2_2)_pX(CR^2_2)_p$ linker of the instant compounds. Thus, the suitably substituted acetyl pyridine **21** is converted to the corresponding pyridinone and undergoes the Ullmann reaction with a suitably substituted phenyl iodide. The acetyl is then brominated to provide intermediate **22**. Reaction with the imidazolyl reagent **5** provides, after deprotection, the instant compound **23**.

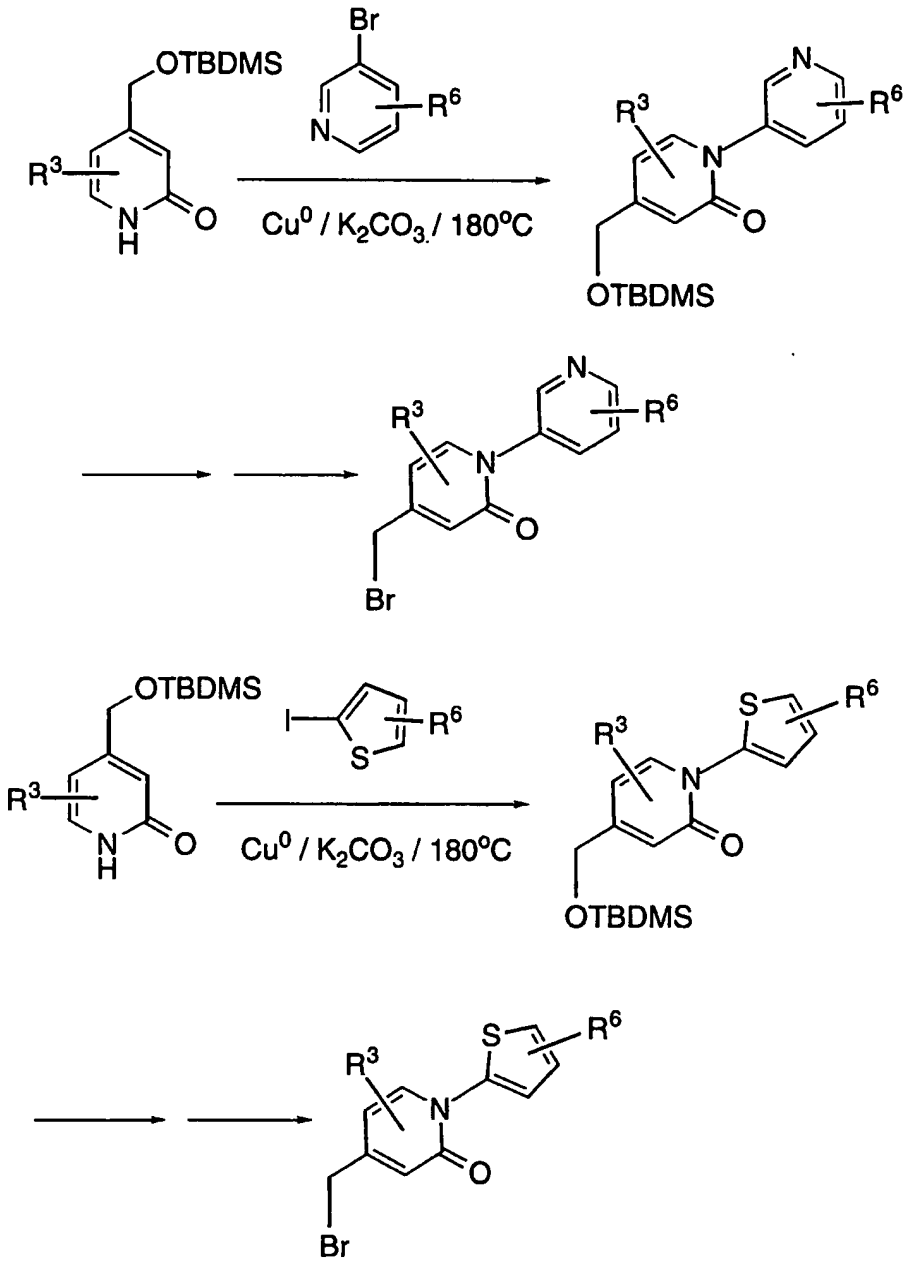
SCHEME 1


COOMe
R3
N
30% H2O2
HOAc / Δ
COOMe
R3
N+
O-
Ac2O / 160°C
1
COOMe
R3
N
H
O
LiBH4 / THF
OH
R3
N
H
O
TBDMSCl
imidazole /DMF
2
OTBDMS
R3
N
H
O
I
R6
Cu0 / K2CO3 / 180°C
R3
N
O
R6
OTBDMS

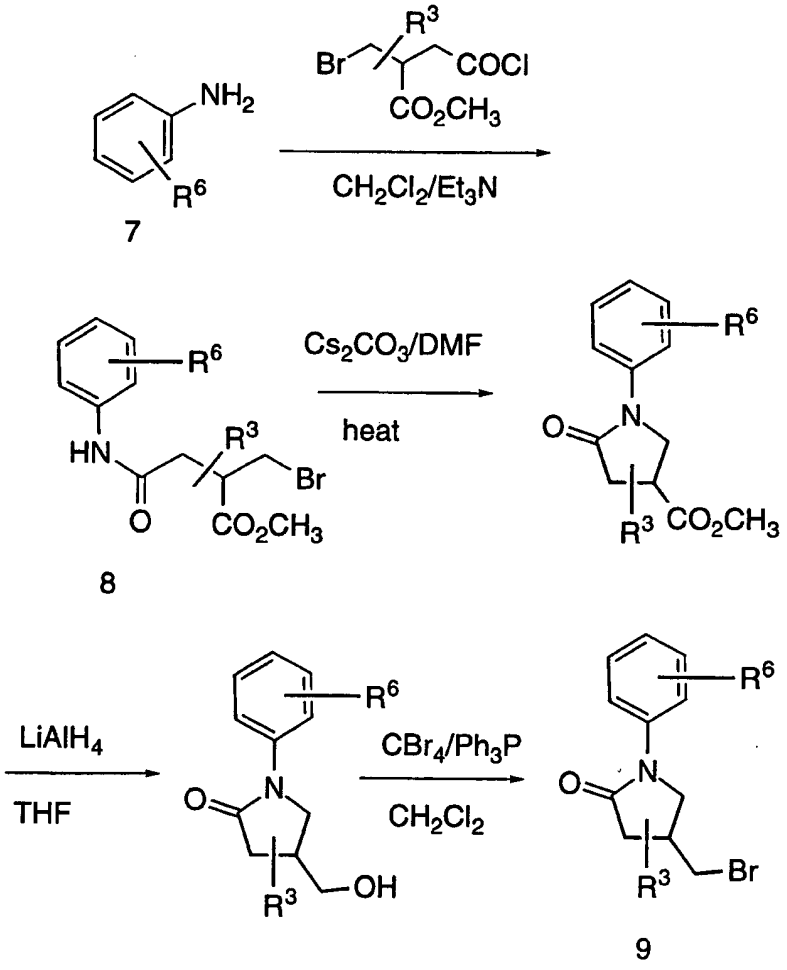
SCHEME 1 (continued)



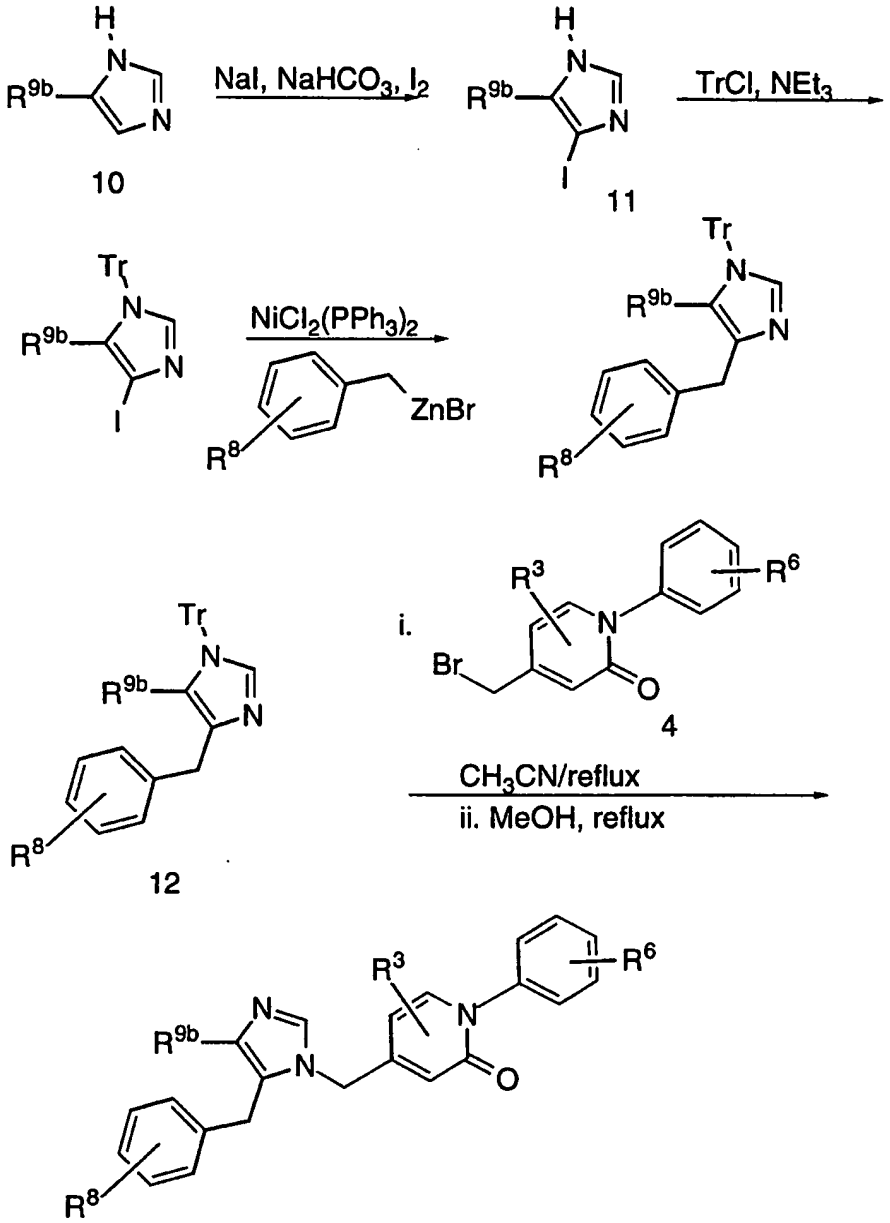
SCHEME 2



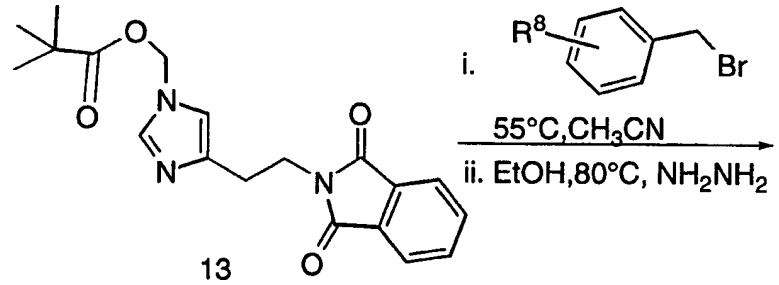
SCHEME 3


NH2
R6
7
R3
Br
COCl
CO2CH3
CH2Cl2/Et3N
HN
O
Br
CO2CH3
8
Cs2CO3/DMF
heat
N
R3
LiAlH4
THF
OH
CBr4/Ph3P
CH2Cl2
9

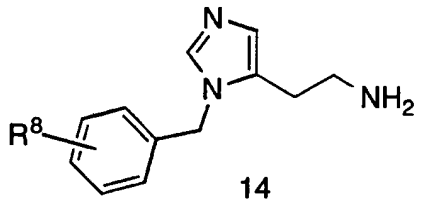
SCHEME 4


NaI, NaHCO3, I2
TrCl, NEt3
10
11
NiCl2(PPh3)2
ZnBr
i.
Br
4
CH3CN/reflux
ii. MeOH, reflux
12

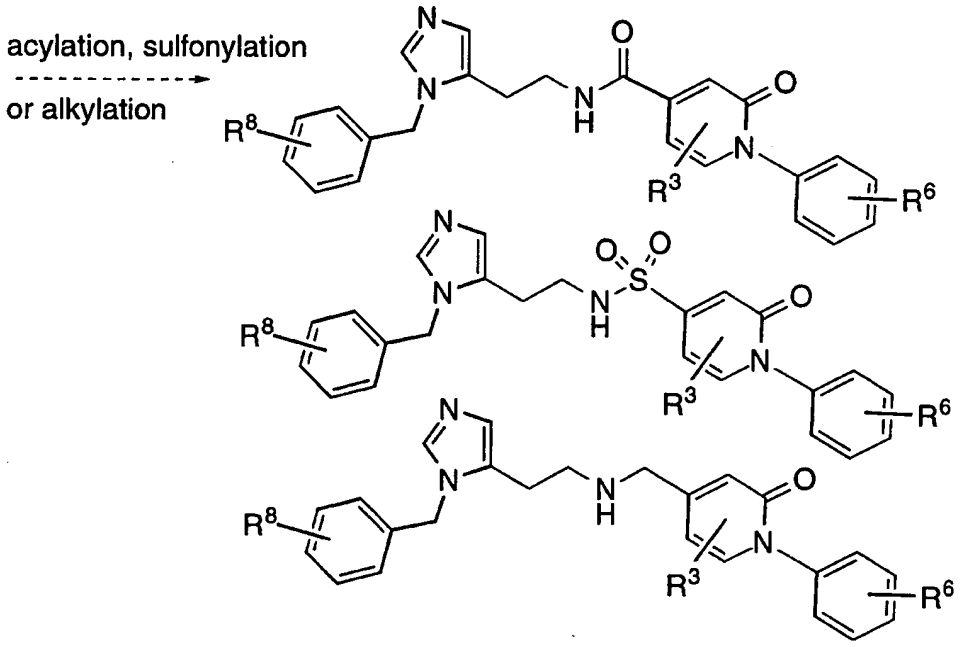
SCHEME 5



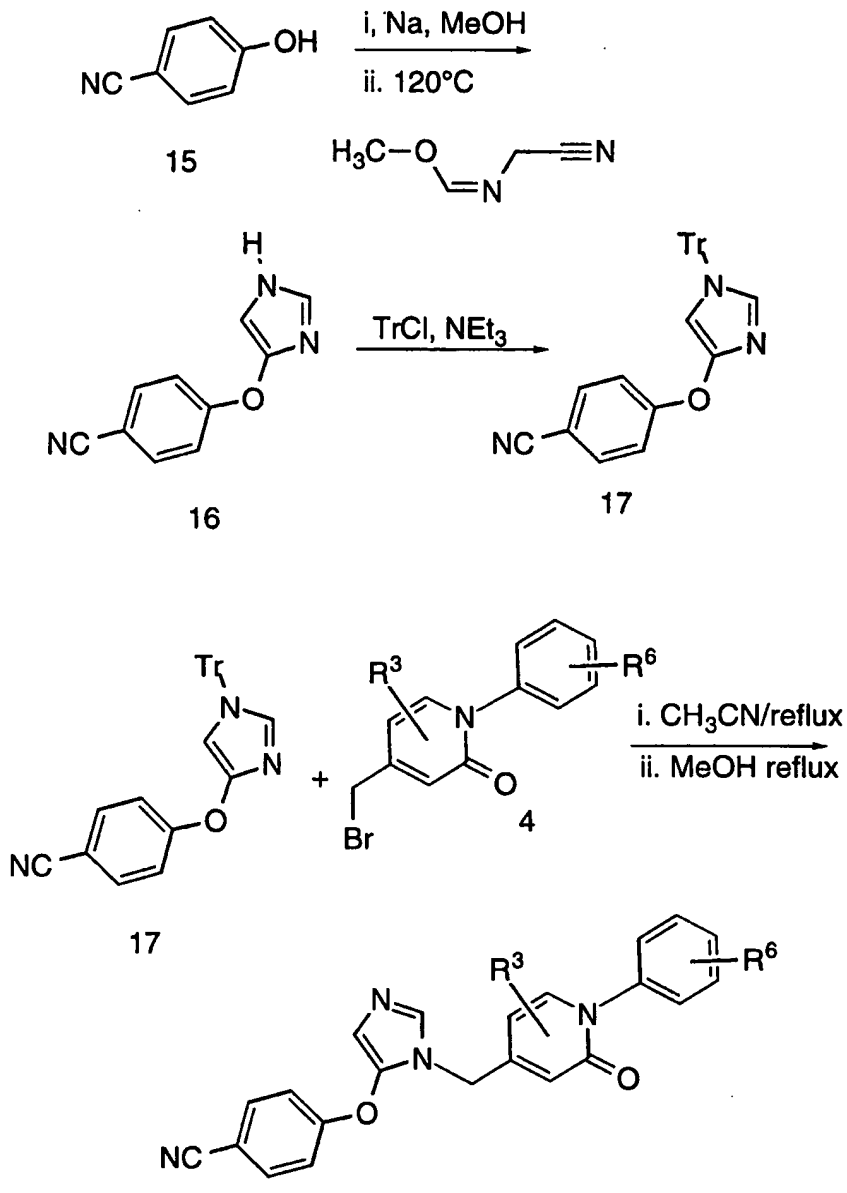
13



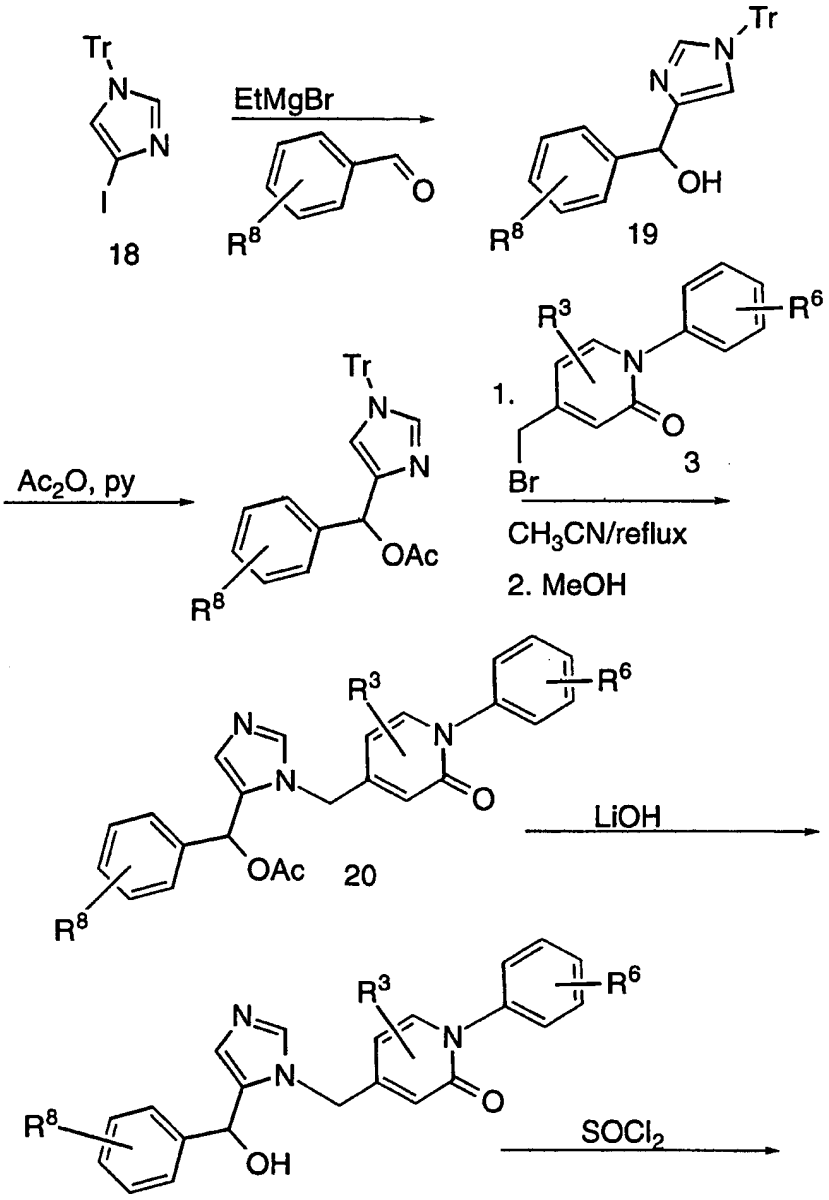
14



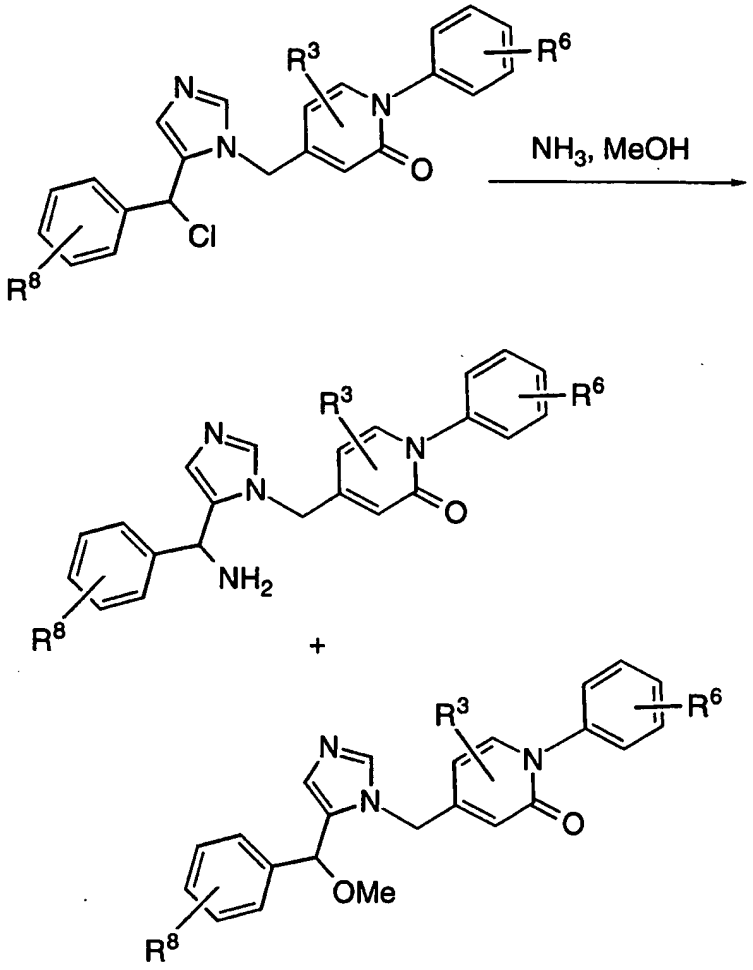
SCHEME 6


i, Na, MeOH
ii. 120°C
15
H_3C-O
N
TrCl, NEt_3
16
17
i. CH_3CN/reflux
ii. MeOH reflux
4
Br
17

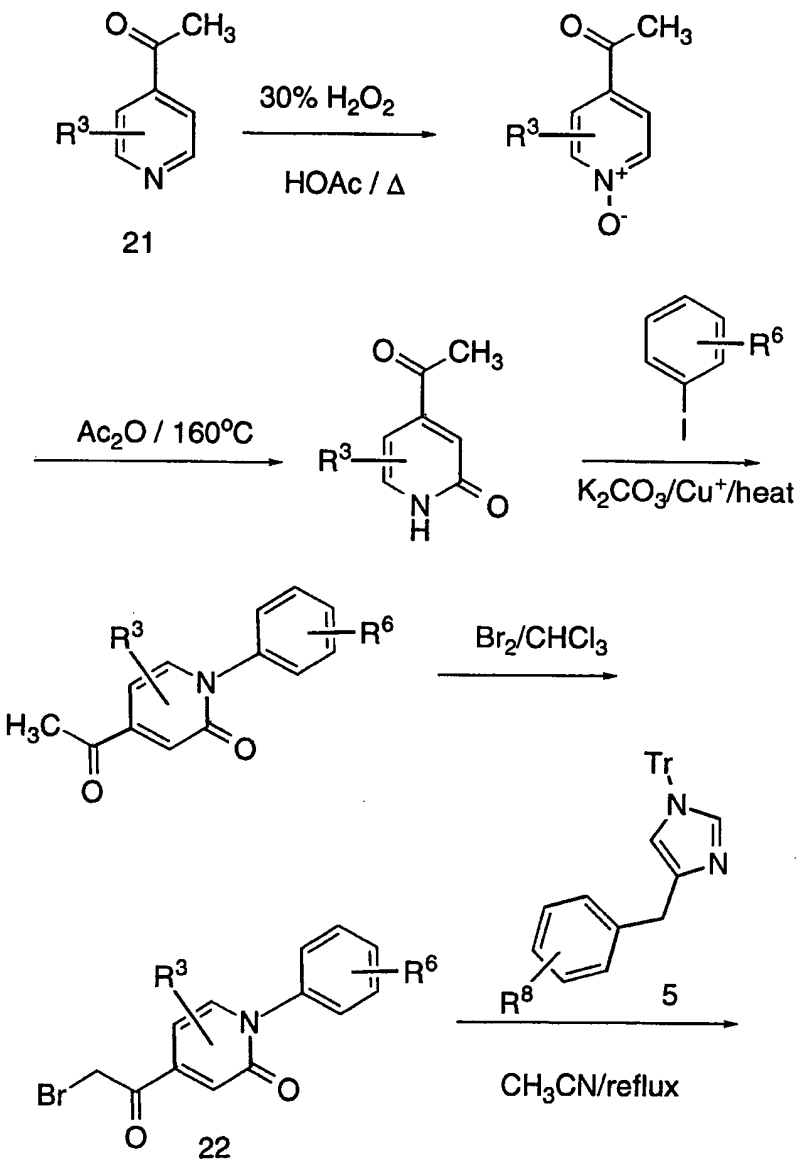
SCHEME 7


Tr
N
N
I
18
EtMgBr
O
R8
Tr
N
N
OH
R8
19
R3
R6
1.
N
O
Br
3
CH3CN/reflux
2. MeOH
Ac2O, py
Tr
N
N
OAc
R8
R3
R6
N
N
N
O
OAc
20
R8
LiOH
R3
R6
N
N
N
O
R8
OH
SOCl2

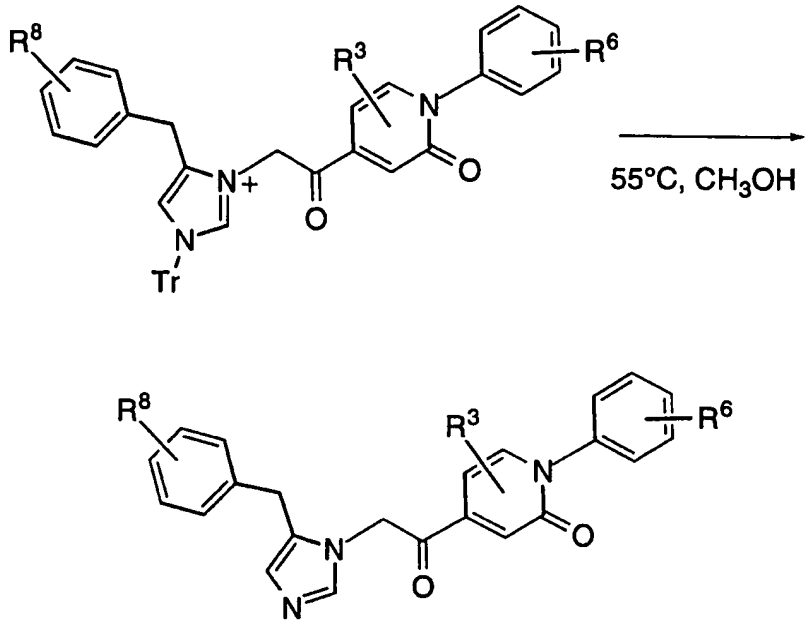
SCHEME 7 (continued)



SCHEME 8

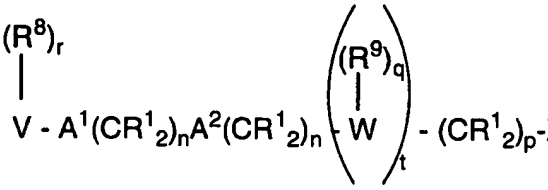

30% H_2O_2
HOAc / Δ
21
Ac_2O / 160°C
K_2CO_3/Cu^+/heat
$Br_2/CHCl_3$
Tr
5
CH_3CN/reflux
22

SCHEME 8 (continued)



23

Schemes 9-17 illustrate reactions wherein the moiety



incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

Thus, the intermediates whose synthesis are illustrated in the Schemes, and other pyridinonecarbocyclic and pyridinoneheterocyclic intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**,

67, 69-75, from the appropriate amino acid. Knochel chemistry may be utilized, as shown in Scheme 9, to incorporate the aryl-pyridinone moiety. Thus, a suitably substituted 4-(bromo)pyridine is converted to the corresponding pyridinone **24** as described above and the pyridinone is coupled to a suitably substituted phenyl iodide as previously described above. The resulting bromide **25** is treated with zinc(0) and the resulting zinc bromide reagent **26** is reacted with an aldehyde to provide the C-alkylated instant compound **27**. Compound **27** can be deoxygenated by methods known in the art, such as a catalytic hydrogention, then deprotected with trifluoro-acetic acid in methylene chloride to give the final compound **28**. The compound **28** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **28** can further be selectively protected to obtain **29**, which can subsequently be reductively alkylated with a second aldehyde to obtain compound **30**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **31** can be accomplished by literature procedures.

If the arylpyridinone zinc bromide reagent is reacted with an aldehyde which also has a protected hydroxyl group, such as **32** in Scheme 10, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 10, 11). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as alkyl lithium reagents, to obtain secondary alcohols such as **34**. In addition, the fully deprotected amino alcohol **35** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **36** (Scheme 11), or tertiary amines.

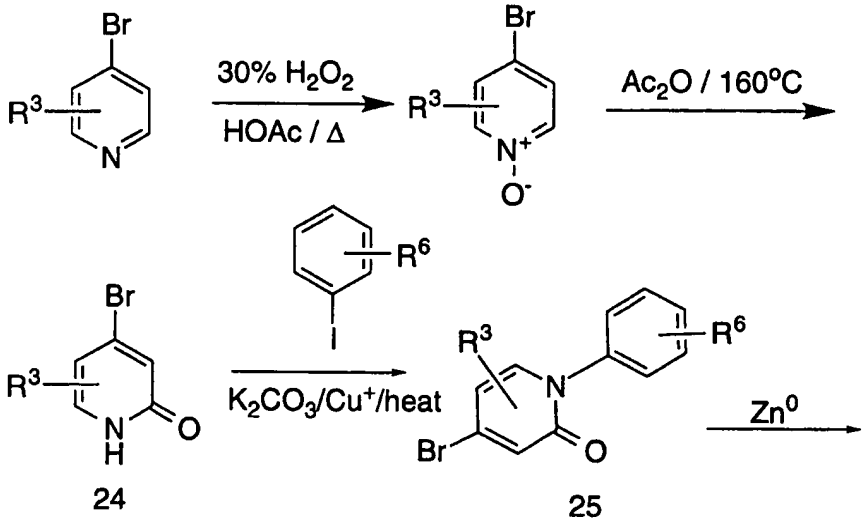
The Boc protected amino alcohol **33** can also be utilized to synthesize 2-aziridinylmethylarylheteroaryl such as **37** (Scheme 12). Treating **33** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of

aziridine **37**. The aziridine is reacted with a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **38** .

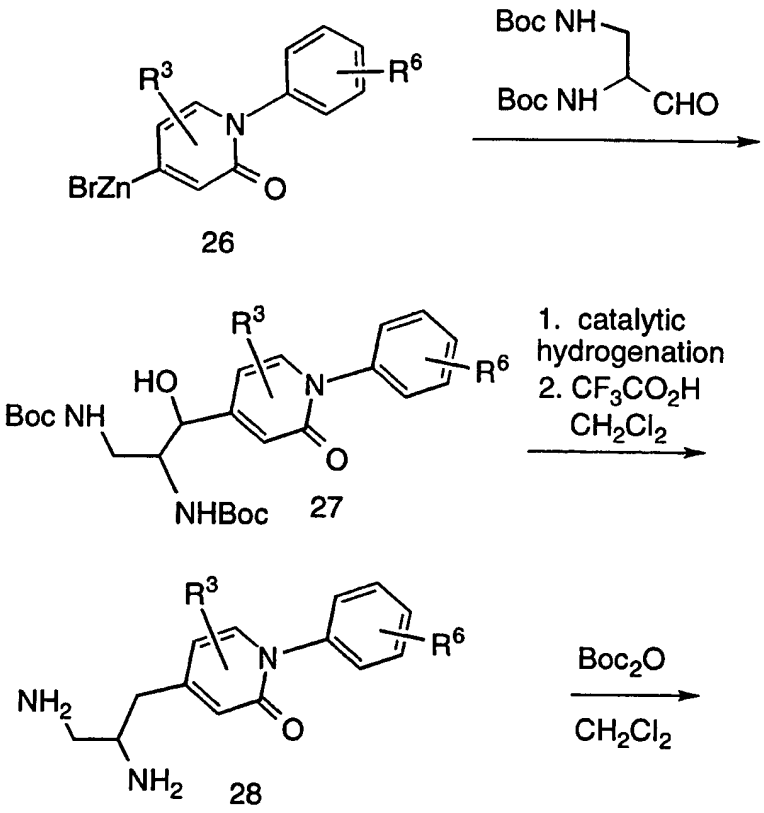
In addition, the arylpyridinone reagent can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **40**, as shown in Scheme 13. When R' is an aryl group, **40** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **41**. Alternatively, the amine protecting group in **40** can be removed, and O-alkylated phenolic amines such as **42** produced.

Schemes 14-17 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

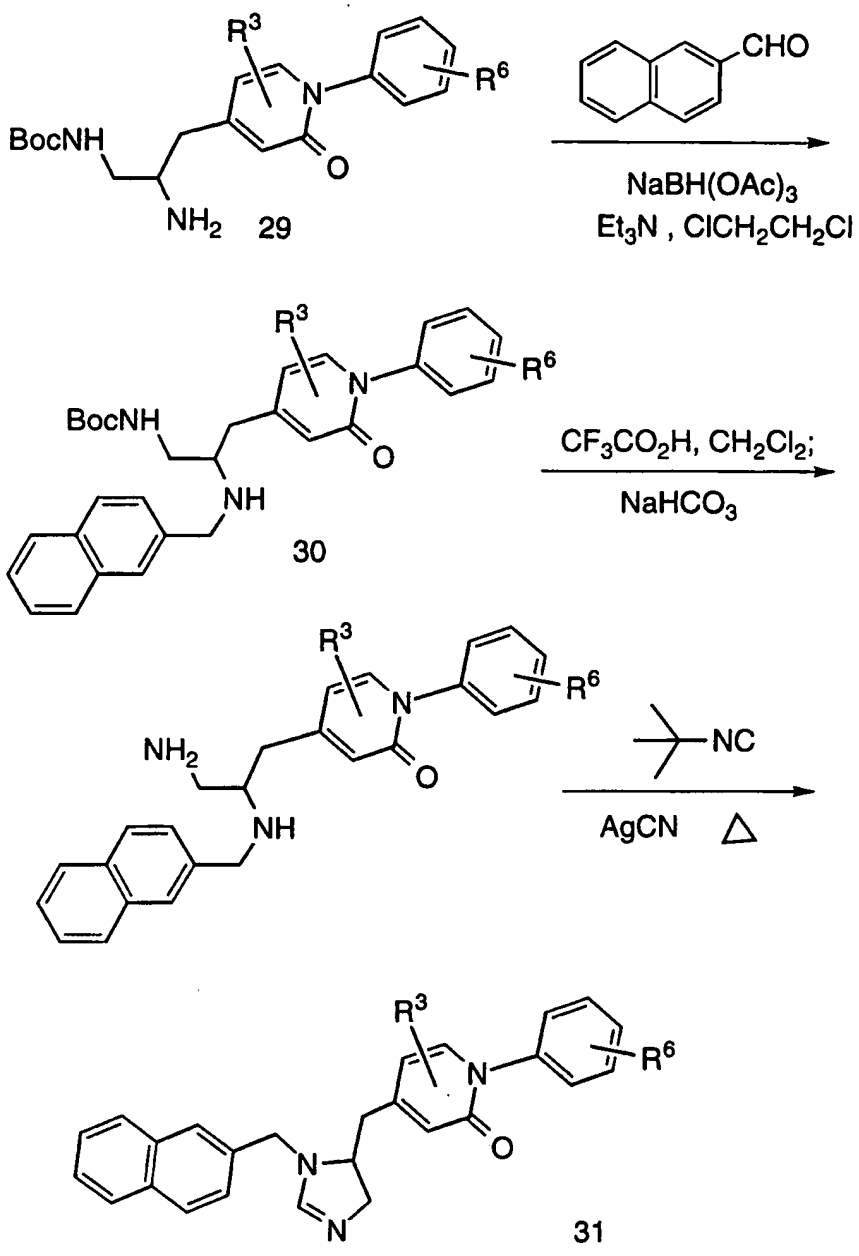
SCHEME 9



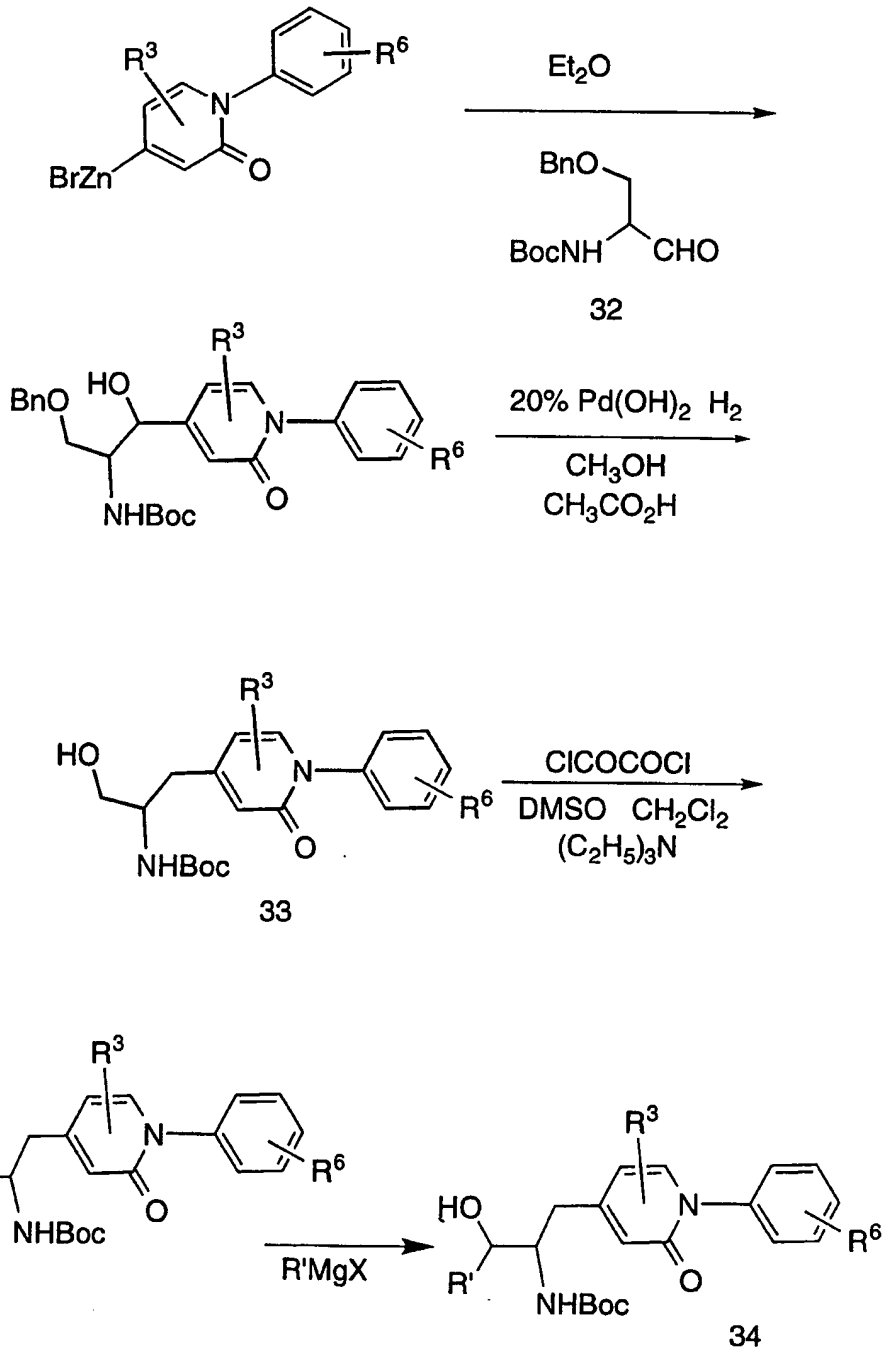
SCHEME 9 (continued)



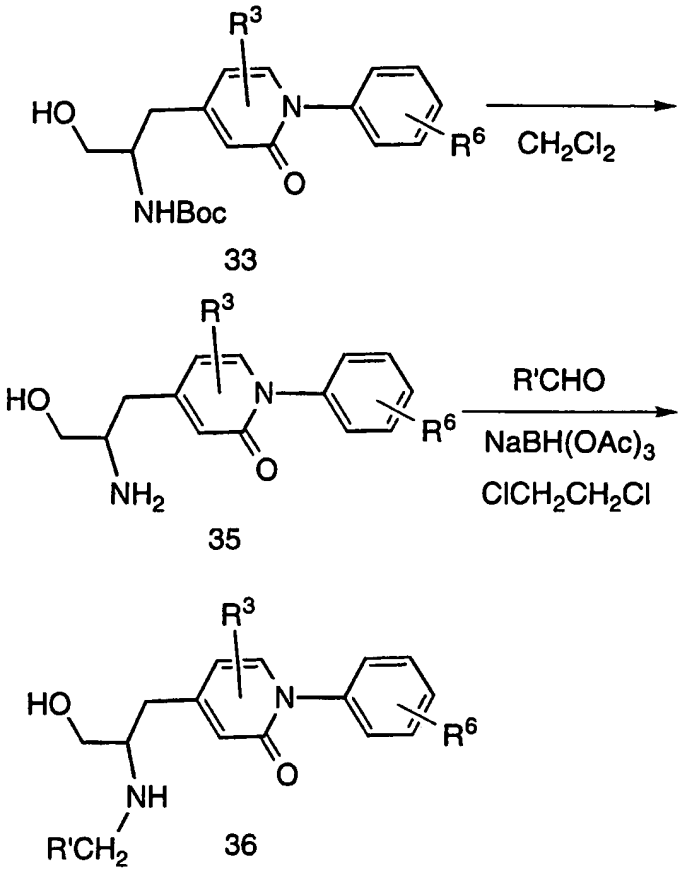
SCHEME 9 (continued)



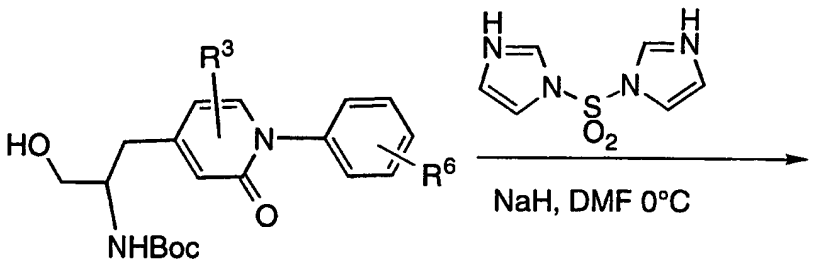
SCHEME 10

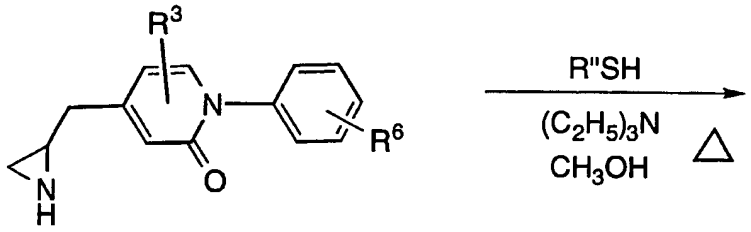

R3
R6
N
O
BrZn
Et2O
BnO
BocNH
CHO
32
HO
BnO
NHBoc
20% Pd(OH)2 H2
CH3OH
CH3CO2H
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N
33
H
R'MgX
R'
34

SCHEME 11

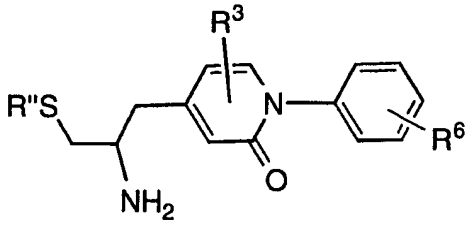

R3
HO
N
R6
CH2Cl2
NHBoc
33
R3
HO
N
R6
R'CHO
NaBH(OAc)3
ClCH2CH2Cl
NH2
35
R3
HO
N
R6
NH
R'CH2
36

SCHEME 12



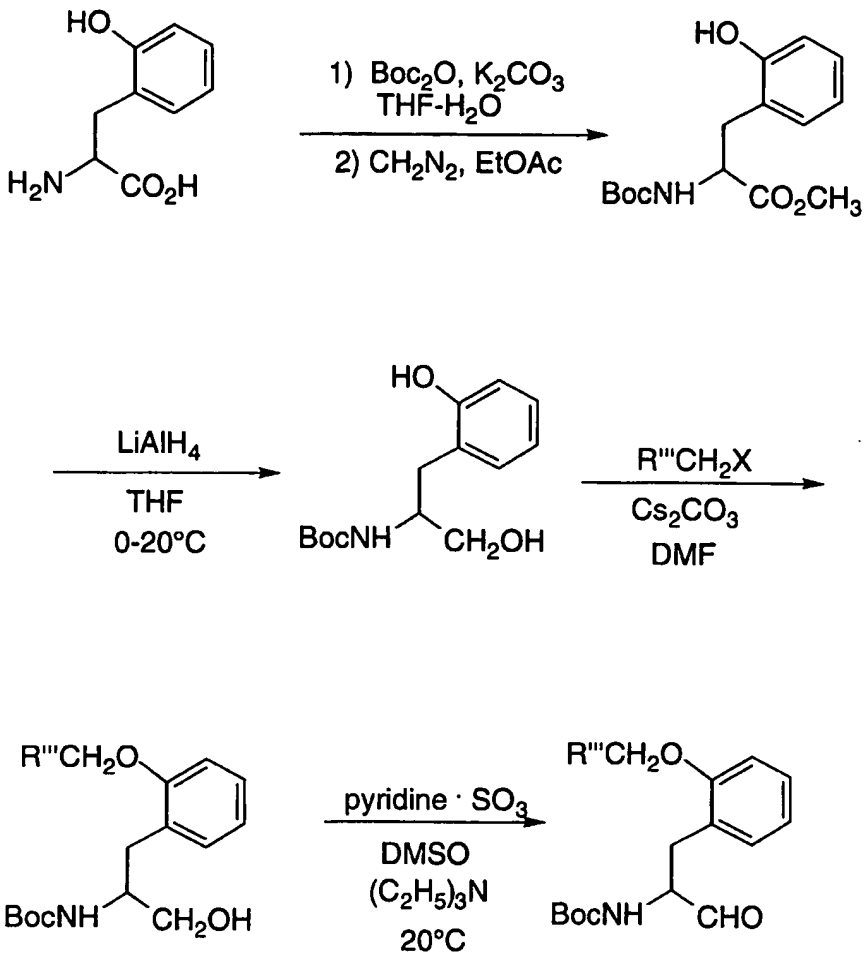


37



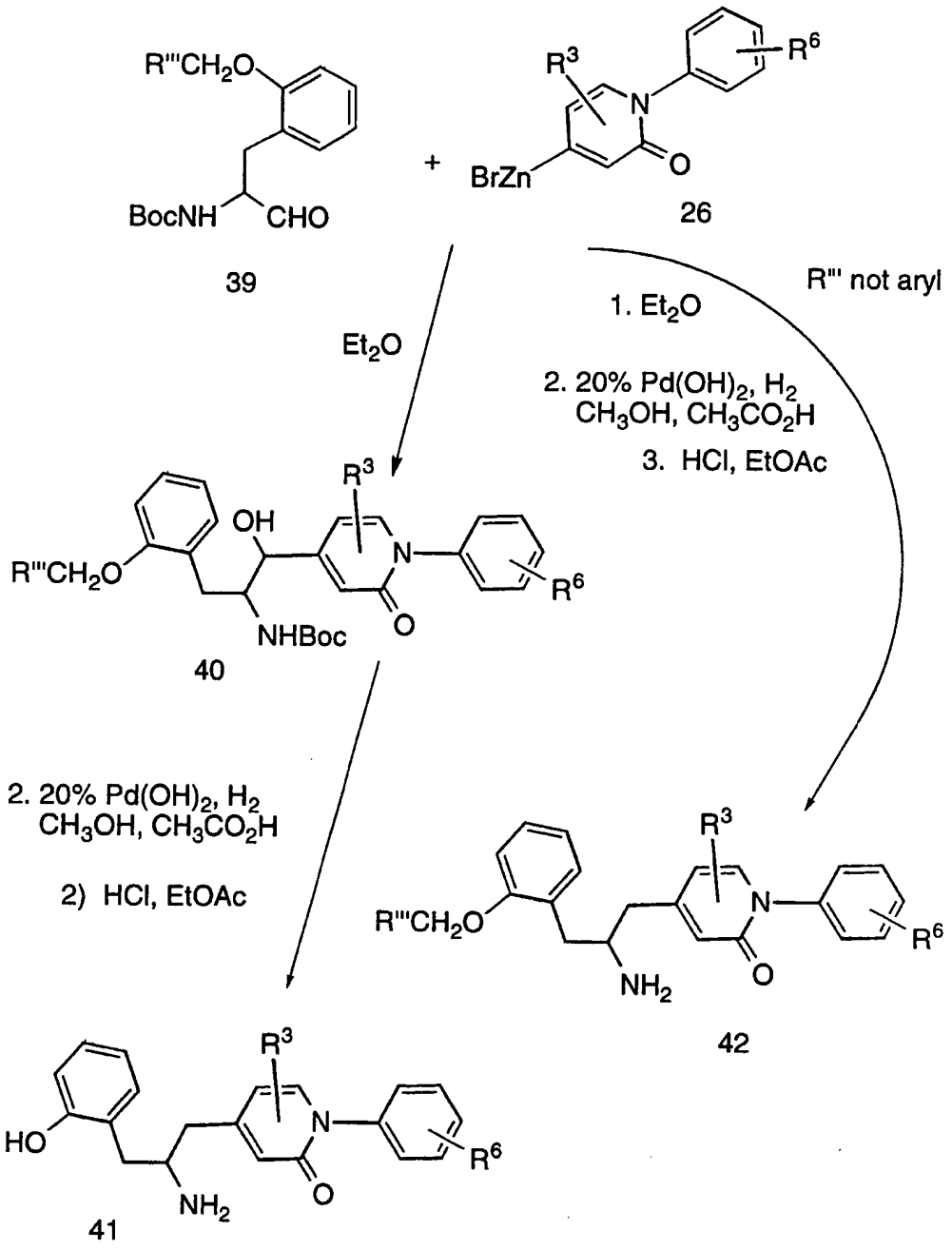
38

SCHEME 13

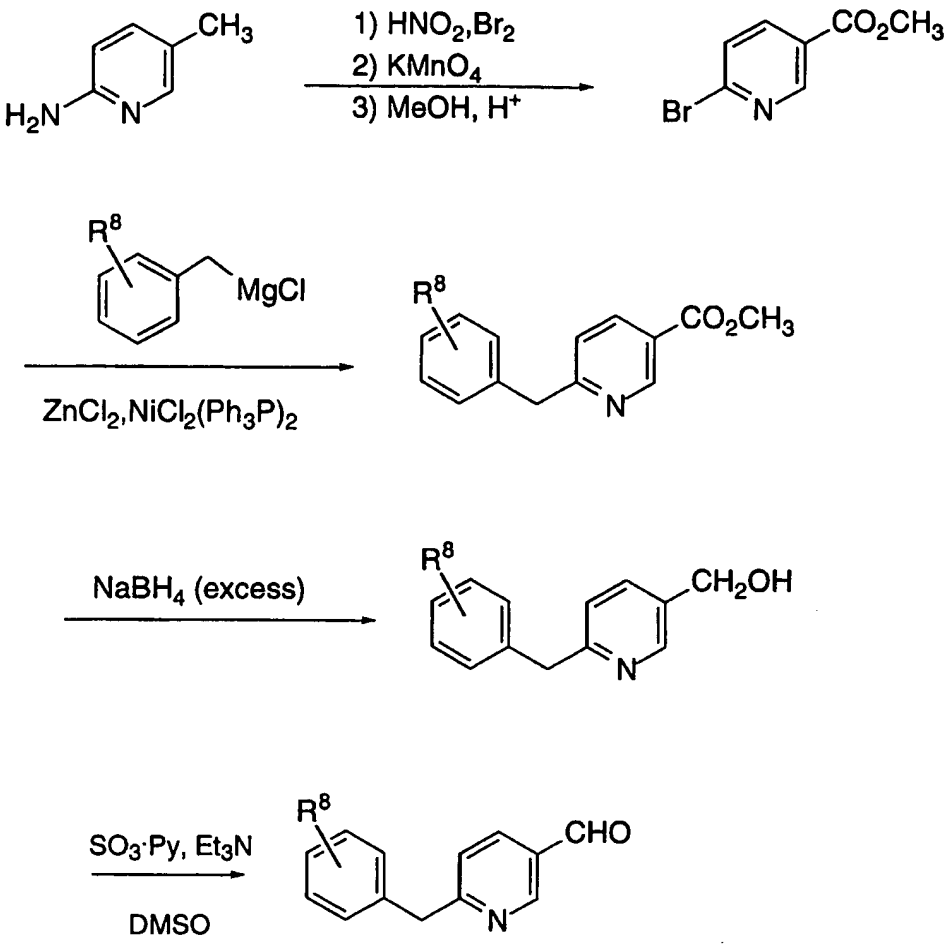

HO
H2N
CO2H
1) Boc2O, K2CO3
THF-H2O
2) CH2N2, EtOAc
HO
BocNH
CO2CH3
LiAlH4
THF
0-20°C
HO
BocNH
CH2OH
R'''CH2X
Cs2CO3
DMF
R'''CH2O
BocNH
CH2OH
pyridine · SO3
DMSO
(C2H5)3N
20°C
R'''CH2O
BocNH
CHO

5

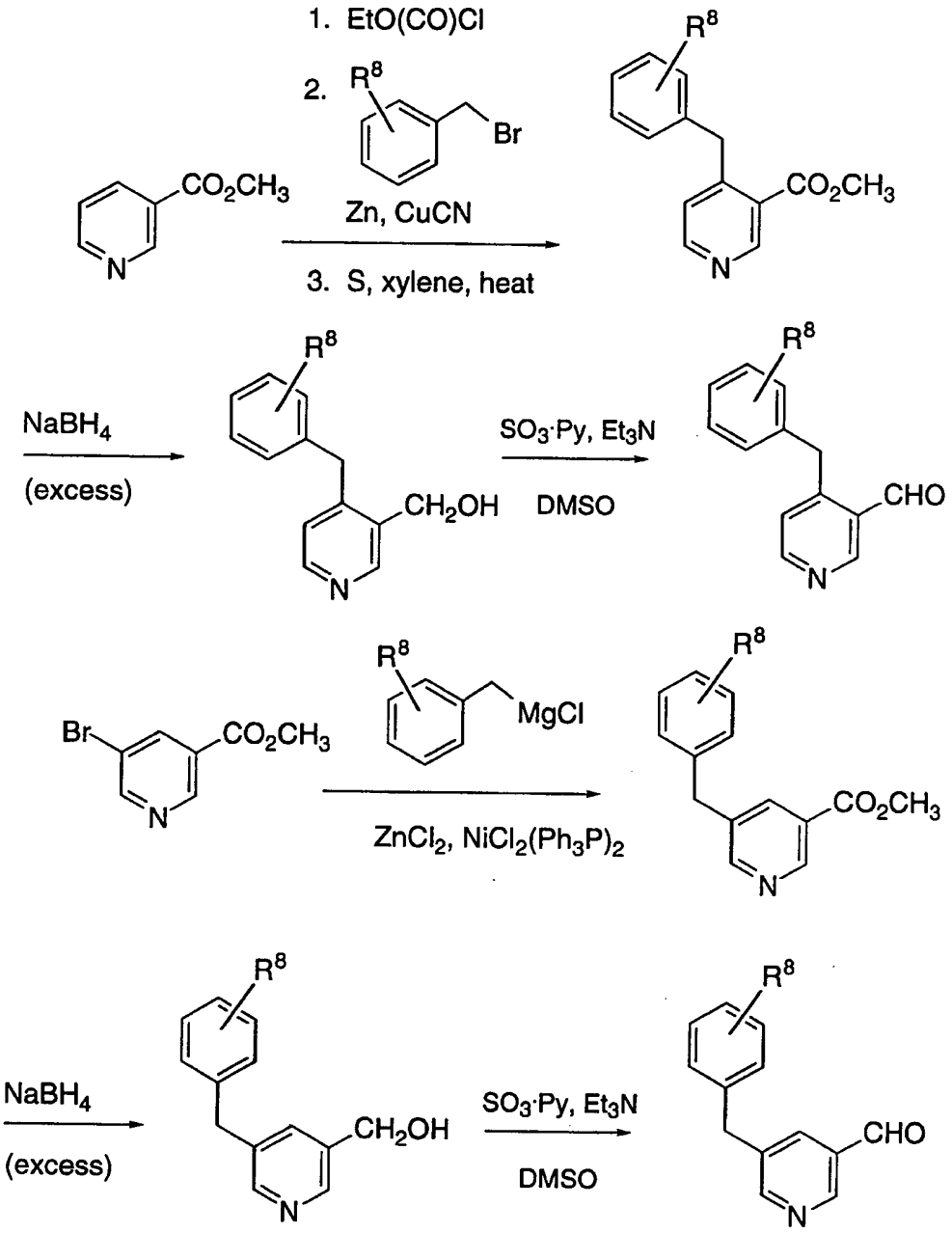
SCHEME 13 (continued)



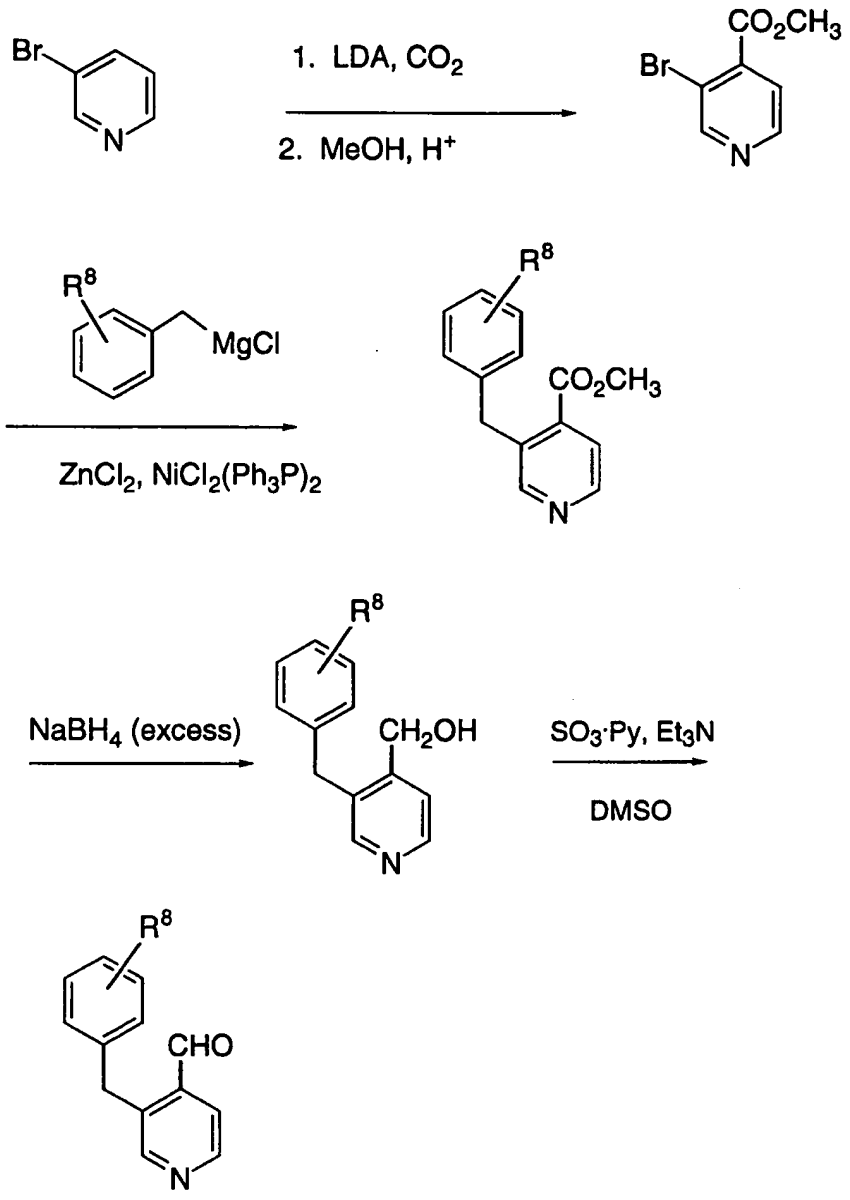
SCHEME 14


CH3
H2N
N
1) HNO2,Br2
2) KMnO4
3) MeOH, H+
CO2CH3
Br
N
R8
MgCl
ZnCl2,NiCl2(Ph3P)2
R8
CO2CH3
N
NaBH4 (excess)
R8
CH2OH
N
SO3·Py, Et3N
DMSO
R8
CHO
N

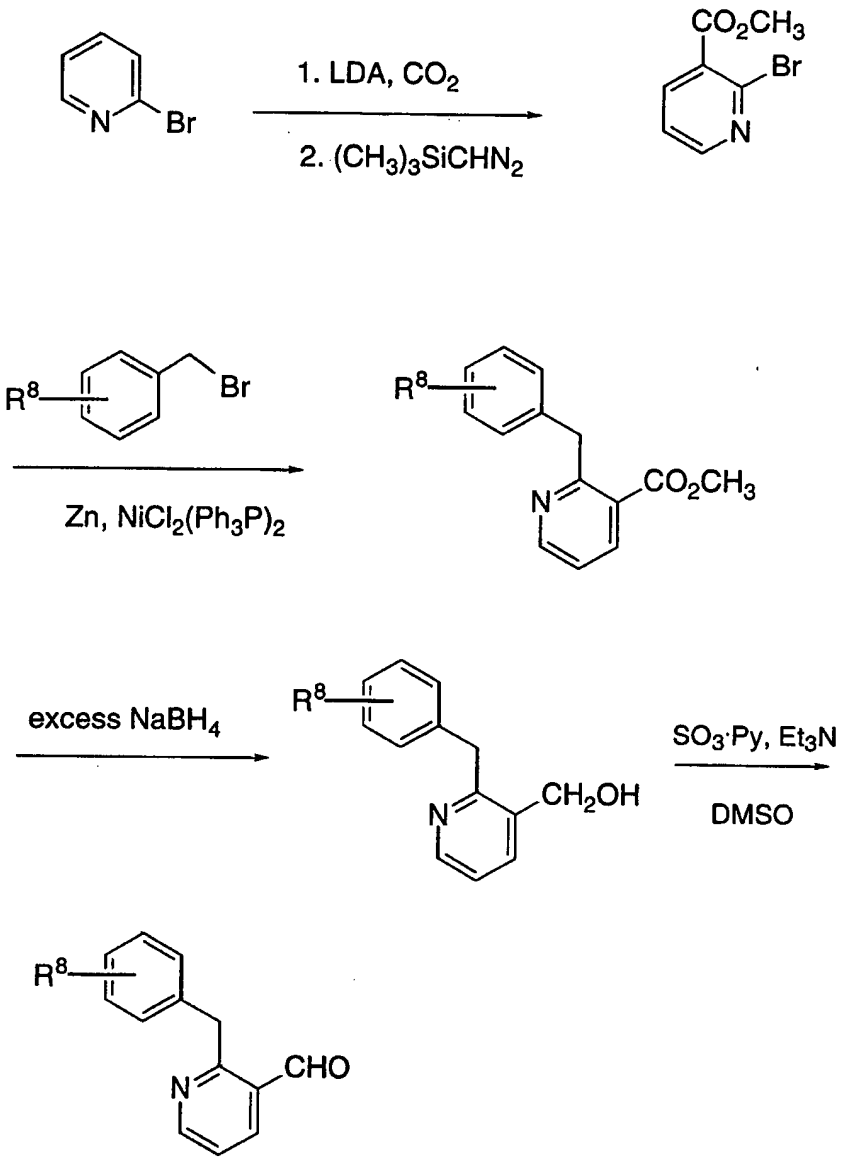
SCHEME 15


1. EtO(CO)Cl
2.
Br
Zn, CuCN
3. S, xylene, heat
NaBH4
(excess)
SO3·Py, Et3N
DMSO
MgCl
ZnCl2, NiCl2(Ph3P)2

SCHEME 16


Br
N
1. LDA, CO_2
2. MeOH, H^+
CO_2CH_3
Br
N
R^8
MgCl
$ZnCl_2$, $NiCl_2(Ph_3P)_2$
R^8
CO_2CH_3
N
$NaBH_4$ (excess)
R^8
CH_2OH
N
SO_3·Py, Et_3N
DMSO
R^8
CHO
N

SCHEME 17



The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine

pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55: 4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al. *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al.*FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

The instant compounds may also be useful as inhibitors of proliferation of vascular smooth muscle cells and therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, restinosis, polycystic kidney

disease, infections of hepatitis delta and related viruses and fungal infections. The instant compounds may also be useful in combination with other inhibitors of parts of the signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Thus, the instant compounds may be utilized in combination with farnesyl pyrophosphate competitive inhibitors of the activity of farnesyl-protein transferase or in combination with a compound which has Raf antagonist activity.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for

cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one

that has a Ki substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile

Step 1: 4-Hydroxymethyl-1H-pyridin-2-one

2-Oxo-1,2-dihydropyridine-4-carboxylic acid methyl ester (1.8g, 12.2 mmol) , prepared as described in *J. Org. Chem.*, 26, 428 (1961), was suspended in THF(100ml). A small amount of DMF was added to help increase solubility. $LiBH_4$ (61 mmol) was added and the reaction was stirred for 18 hours at room temperature. MeOH and H_2O are added to quench the reaction. The reaction is then concentrated to yield a yellow oil. Flash chromatography (5% MeOH/$CHCl_3$ to 20% MeOH/$CHCl_3$) yielded 4-hydroxymethyl-1H-pyridin-2-one as a white solid.

^1H NMR (400 MHz, CD_3OD) δ 7.38-7.36 (1H,d); 6.56 (s, 1H); 6.37-6.36 (d, 1H); 4.50 s, 2H).

Step 2: 4-(tert-butyldimethylsilyloxymethyl)-1H-pyridin-2-one

4-Hydroxymethyl-1H-pyridin-2-one from Step 1 (1.3g, 10.5 mmol) was dissolved in DMF. t-Butyl dimethylsilyl chloride (12.6 mmol, 1.9g) and imidazole (12.6 mmol, 858 mg) were added and the

reaction was stirred for 16 hours. The reaction mixture was diluted with EtOAc and washed with H_2O (2x) and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to yield a yellow oil. Flash chromatography (EtOAC) yielded 4-(tert-butyldimethylsilyloxy-methyl)-1H-pyridin-2-one as an off white solid.
^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.28 (d, 1H); 6.60 (s, 1H); 6.20-6.18 (d, 1H); 4.58 (s, 2H); 0.955 (s, 9H); 0.11 (s, 6H).

Step 3: 4-(tert-butyl-dimethyl-silanyloxymethyl)-1-phenyl-1H-pyridin-2-one

4-(Tert-butyldimethylsilyloxymethyl)-1H-pyridin-2-one from Step 2 (1.5g, 6.3 mmol) was dissolved in iodobenzene (189 mmol, 21.12 mL) and treated with copper (6.3 mmol, 400 mg) and K_2CO_3 (6.93 mmol, 958 mg.). The brown slurry was heated to 180° for 16 hrs. The reaction mixture was cooled, diluted with $CHCl_3$ and washed with saturated $NaHCO_3$. The aqueous layer was back extracted with $CHCl_3$ (2x). The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to yield a yellow oil. Flash Chromatography (20% EtOAc/Hexane) yielded 4-(tert-butyl-dimethyl-silanyloxymethyl)-1-phenyl-1H-pyridin-2-one as a white solid.
^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H); 7.43-7.39 (m, 3H); 7.29-7.28 (d, 2H); 6.65 (s, 1H); 6.19 (d, 2H); 4.59 (s, 2H); 0.97 (s, 9H); 0.14 (s, 6H).

Step 4: 4-Hydroxymethyl-1-phenyl-1H-pyridin-2-one

4-(Tert-butyl-dimethyl-silyloxymethyl)-1-phenyl-1H-pyridin-2-one from Step 3 (1.3g) was dissolved in TBAF in 1M THF (15 mL). The clear reaction mixture was stirred for 16 hours. The reaction mixture was concentrated and purified on a column of silica eluting with 10% MeOH/EtOAc to yield 4-hydroxymethyl-1-phenyl-1H-pyridin-2-one as a tan solid.
^1H NMR (400 MHz, $CDCl_3$) δ 7.5-7.47 (m, 2H); 7.43 (d, 1H); 7.38-7.36 (m, 2H); 7.32-7.30 (d, 1H) 6.67 (s, 1H); 6.23 (d, 1H) 4.57 (d, 2H).

Step 5: 4-Bromomethyl-1-phenyl-1H-pyridin-2-one

4-Hydroxymethyl-1-phenyl-1H-pyridin-2-one from Step 4 (1.0g, 5 mmol) was dissolved in CH_2Cl_2. CBr_4 (6 mmol, 2g) was added and the reaction mixture was cooled to 0°. PPh_3 (6 mmol, 2.0 g) was added dropwise in CH_2Cl_2. The reaction mixture was stirred at 0° for 15 minutes and then warmed to room temperature. The reaction mixture was concentrated and purified on a column of silica eluting with (30 % EtOAc /hexane to 50% EtOAc/hexane) to give 4-bromomethyl-1-phenyl-1H-pyridin-2-one (8 ,x=H) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H); 7.45-7.43 (d, 1H); 7.38-7.33 (m, 3H); 6.64 (s, 1H); 6.30-6.28 (d, 1H); 4.25 (d, 2H).

Step 6: 4-(1-Trityl-1H-imidazol-4-ylmethyl)-benzonitrile

To a suspension of activated zinc dust (3.57g, 54.98 mmol) in THF (50 mL) was added dibromoethane (0.315 mL, 3.60 mmol) and the reaction stirred under argon for 45 minutes, at 20°C. The suspension was cooled to 0°C and α-bromo-p-tolunitrile (9.33g, 47.6 mmol) in THF (100 mL) was added dropwise over a period of 10 minutes. The reaction was then allowed to stir at 20°C for 6 hours and bis(triphenyl-phosphine)Nickel II chloride (2.40g, 3.64 mmol) and 5-iodotrityl imidazole (15.95g, 36.6 mmol) were added in one portion. The resulting mixture was stirred 16 hours at 20°C and then quenched by addition of saturated NH4Cl solution (100 mL) and the mixture stirred for 2 hours. Saturated aq. $NaHCO_3$ solution was added to give a pH of 8 and the solution was extracted with EtOAc (2 x 250 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed (silica gel, 0-20% EtOAc in CH2Cl2) to afford the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400Mz) δ (7.54 (2H, d, J=7.9Hz), 7.38(1H, s), 7.36-7.29 (11H, m), 7.15-7.09(6H, m), 6.58(1H, s) and 3.93(2H, s) ppm.

Step 7: 4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride

4-Bromomethyl-1-phenyl-1H-pyridin-2-one from Step 5 (1.1g, 4.1 mmol) and 4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile from Step 6 (4.1 mmol, 1.7g) were suspended in CH_3CN and heated to 80°. After 30 minutes the reaction became homogeneous. The reaction mixture was heated to 80° for 16 hours. The heterogeneous reaction mixture was concentrated, taken up in MeOH and refluxed for 1 hour. The reaction mixture was cooled, diluted with $CHCl_3$ and washed with saturated $NaHCO_3$. The aqueous layer was back extracted 4 times with $CHCl_3$. The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to yield a yellow solid which was purified by flash chromatography (7% i-PrOH/$CHCl_3$ saturated with NH_3). Purest fractions were collected and concentrated to yield a white solid which was triturated with EtOAc. The solids were filtered, washed with EtOAc and dried under hi-vacuum for 16 hours to yield 4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H); 7.58-757 (d, 2H) 7.52-7.49 (m, 2H); 7.46-7.44 (d, 1H); 7.34-7.32 (d, 2H); 7.26-7.25 (m, 2H); 6.97 (s, 1H); 6.20 (s, 1H); 5.77 (d, 1H); 4.77 (d, 2H); 3.96 (s, 2H).

EXAMPLE 2

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 3-chloroiodobenzene for the iodobenzene in Step 3.

^1H NMR (400 MHz, DMSO d_6) δ 9.25 (s, 1H); 7.73-7.71 (d, 2H); 7.61-7.58 (m, 2H); 7.54-7.52(m, 2H); 7.46 (s, 1H); 7.38-7.36 (d, 2H); 7.30 (m, 1H); 6.07-6.05 (d, 1H); 5.87 (s, 1H); 5.34 (s, 2H); 4.20 (s, 2H).

EXAMPLE 3

4-[3-(2-Oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile hydrochloride salt was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-bromopyridine for the iodobenzene in Step 3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H); 8.60-8.59 (d, 1H); 8.00-7.96 (t, 1H); 7.81-7.79(d, 1H); 7.71-7.69 (d, 3H); 7.64 (s, 1H); 7.51-7.48 (m, 1H); 7.37-7.35 (d, 2H); 6.11-6.09 (d, 1H); 5.91 (s, 1H); 5.36 (s, 2H); 4.20 (s, 2H).

EXAMPLE 4

4-[3-(6'-Methyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-bromo-6-methylpyridine for the iodobenzene in Step 3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.79 (d, 1H); 7.75-7.71 (m, 1H); 7.68-7.61 (d, 1H); 7.58-7.56(m, 3H); 7.1-7.24 (m, 3H); 6.96 (s, 1H); 6.12 (s, 1H); 5.83-5.81(dd, 1H); 4.75 (s, 2H); 3.92 (s, 2H); 2.58 (s, 3H).

EXAMPLE 5

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}-2-methoxy-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, but substituting 4-(1-trityl-1H-imidazol-4-ylmethyl)-3-methoxybenzonitrile for 4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile in Step 7.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (br s, 1H); 7.48-7.41 (m, 3H); 7.36 (s, 1H); 7.02(br s, 1H); 6.80-6.78 (d, 1H); 6.69 (s, 1H); 6.14 (s, 1H); 5.77-5.75 (dd, 1H); 4.77 (s, 2H); 3.92 (s, 2H); 3.86 (s, 3H).

EXAMPLE 6

4-[3-(2-Oxo-1-pyrimidin-2-yl-1,2-dihydro-pyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-chloropyrimidine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, 2H); 7.58-7.55 (m, 3H); 7.50-7.48 (d, 1H); 7.42-7.40(t, 1H); 7.22-7.20 (d, 2H); 6.98 (s, 1H); 6.20 (s, 1H); 5.74-5.71 (dd, 1H); 4.77 (s, 2H); 3.92 (s, 2H).

EXAMPLE 7

4-{3-[1-(6-chloro-pyrazin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2,6-dichloropyrazine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H); 8.61 (s, 1H); 7.88-7.86 (d, 1H); 7.58-7.63(m, 3H); 7.24-7.21 (d, 2H); 6.98 (s, 1H); 6.08 (s, 1H); 5.92-5.90 (dd, 1H); 4.76 (s, 2H); 3.92 (s, 2H).

EXAMPLE 8

4-[3-(3'-Methyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile,

hydrochloride, but substituting 2-bromo-3-mehtylpyridine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.44 (D, 1H); 7.71-7.69 (d, 1H); 7.60-7.57 (m, 3H); 7.36-7.29(m, 2H); 7.25-7.23 (d, 2H); 6.96 (s, 1H); 6.15 (s, 1H); 5.82-5.80 (dd, 1H); 4.78 (s, 2H); 3.93-3.92 (d, 2H); 2.22 (s, 3H).

EXAMPLE 9

4-[3-(6'-chloro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2,6-dichloropyridine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (dd, 1H); 7.88-7.86 (d, 1H); 7.84-7.80 (t, 1H); 7.57-7.55 (m, 3H); 7.38-7.35 (dd, 1H); 7.23-7.21 (d, 2H); 6.97 (s, 1H); 5.88-5.86 (dd, 1H); 4.75 (s, 2H); 3.92 (s, 2H).

EXAMPLE 10

4-[3-(6-'Triflouromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-chloro-6-trifluoromethylpyridine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.25 (d, 1H); 8.06-8.02 (t, 1H); 7.97-7.95 (d, 1H); 7.72-7.70(d, 1H); 7.57-7.55 (m, 3H); 7.26-7.22 (m, 2H); 6.98 (s, 1H); 6.05 (s, 1H); 5.93-5.90 (dd, 1H); 4.77 (s, 2H); 3.93 (s, 2H).

EXAMPLE 11

4-{3-[1-(6-Chloro-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2,4-dichloropyrimidine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74-8.72 (d, 1H); 8.31-8.30 (d, 1H); 8.18-8.17 (d, 1H); 7.57-7.55(m, 3H); 7.23-7.21 (d, 2H); 6.99 (s, 1H); 5.99 (s, 1H); 5.94-5.92 (dd, 1H); 4.76 (s, 2H); 3.92 (s, 2H).

EXAMPLE 12

4-{3-[1-(6-Chloro-pyrazin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-2-methoxy-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2,6-dichloropyrazine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H); 8.62 (s, 1H); 7.88-7.86 (d, 1H); 7.58(s, 1H); 7.47-7.44 (d, 1H); 7.01 (1, 1H); 6.78-6.75 (d, 1H); 6.68 (s, 1H); 6.08 (s, 1H); 5.93-5.90 (d, 1H); 4.78 (s, 2H); 3.91 (s, 2H); 3.86 (s, 3H).

EXAMPLE 13

4-{3-[1-(6-Chloro-4-methyl-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2,4-dichloro-6-methylprimidine for the iodobenzene in Step 3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.10 (m, 2H); 7.56-7.54 (d, 3H); 7.22-7.20 (d, 2H); 6.99-(s, 1H); 5.97 (s, 1H); 5.92-5.89 (dd, 1H); 4.75 (s, 2H); 3.92 (s, 2H); 2.63 (d, 3H).

EXAMPLE 14

3-[3-(6'-chloro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4 -[3-(6'-chloro-2-oxo-2H-[1,2'] bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile, but substituting 3-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile for 4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile in Step 7.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.80 (m, 3H); 7.63-7.51 (m, 2H); 7.42-7.29 (m, 4H); 6.95(s, 1H); 6.34 (s, 1H); 5.89-5.87 (d, 1H); 4.78 (s, 2H); 3.90 (s, 2H).

EXAMPLE 15

4-[3-(5'-Cyano-2-oxo-2H-[1,3']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 3-cyano-5-bromopyridine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.81 (m, 2H); 7.56-7.54 (m, 3H); 7.41 (m, 2H), 7.22-7.20 (d, 2H, J=7.9 Hz); 6.99-(s, 1H); 5.96 (s, 1H); 5.91-5.88 (dd, 1H); 4.75 (s, 2H); 3.89 (s, 2H).

EXAMPLE 16

4-[3-(4'-Trifluoromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-

(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-bromo-4-trifluoromethylpyridine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-7.72 (m, 2H); 7.57-7.55 (m, 3H); 7.44 (m, 2H), 7.22-7.20 (d, 2H,J=7.9 Hz); 6.98 (s, 1H); 5.96 (s, 1H); 5.91-5.88 (dd, 1H); 4.74 (s, 2H); 3.88 (s, 2H).

EXAMPLE 17

4-[3-(6'-Methoxy-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-bromo-6-methoxypyridine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-7.72 (m, 2H); 7.57-7.55 (m, 3H); 7.46 (m, 2H), 7.23-7.19 (d, 2H, J=7.9 Hz); 6.98 (s, 1H); 5.96 (s, 1H); 5.90-5.85 (dd, 1H); 4.75 (s, 2H); 3.84 (s, 2H); 3.76 (s, 3H).

EXAMPLE 18

4-[3-(3'-Nitro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-bromo-3-nitropyridine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-7.71 (m, 2H); 7.57-7.55 (m, 3H); 7.52-7.36 (m, 2H), 7.23-7.19 (d, 2H, J=7.9 Hz); 6.98 (s, 1H); 5.95 (s, 1H); 5.90-5.84 (dd, 1H); 4.74 (s, 2H); 3.86 (s, 2H).

EXAMPLE 19

4-[3-(3'-Trifluoromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-chloro-3-trifluoropyridine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-7.73 (m, 2H); 7.58-7.55 (m, 3H); 7.51-7.39 (m, 2H), 7.24-7.18 (d, 2H, J=7.9 Hz); 6.96 (s, 1H); 5.95 (s, 1H); 5.92-5.82 (dd, 1H); 4.73 (s, 2H); 3.84 (s, 2H).

EXAMPLE 20

4-{3-[1-(6-Trifluromethyl-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-yl methyl]-3H-imidazol-4-ylmethyl}-benzonitrile was prepared in a manner substantially similar to the procedure described above for 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride, but substituting 2-chloro-4-trifluoropyrimidine for the iodobenzene in Step 3.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-7.72 (m, 2H); 7.57-7.49 (m, 2H); 7.48-7.39 (m, 2H), 7.26-7.20 (d, 2H, J=7.9 Hz); 6.95 (s, 1H); 5.96 (s, 1H); 5.94-5.83 (dd, 1H); 4.73 (s, 2H); 3.82 (s, 2H).

EXAMPLE 21

4-[5-(4-Bromophenoxy)imidazol-1-ylmethyl]-1-(6-cyanopyrazin-2-yl)-1H-pyridin-2-one

Step 1: 4-(4-Bromophenyloxy)imidazole

To a mixture of liquid 4-bromophenol (25 g, mp 64-68°C) at 100-110°C and its sodium salt [Prepared from 3.5 g (20 mmol) 4-bromo-phenol and sodium metal (0.46 g, 20 mmol) in anhydrous

methanol. The resultant solution was concentrated and the residual solvent removed under vacuum overnight], neat methyl N-(cyano-methyl)methanimidate (2 mL, 20 mmol; Hosmane, R. S. et al, J. Org. Chem., p. 1212, 1984) was added dropwise over a period of 10 minutes under a slow stream of dry argon. The resultant mixture was stirred at 100°C for 2 h, and the reaction product partitioned between methylene chloride (250 mL) and aqueous sodium hydroxide (1 M, 250 mL). The aqueous layer was separated and extracted with methylene chloride (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over anhydrous potassium carbonate, filtered and concentrated. The residue was subjected to column chromatography on silica gel eluting with a mixture of 7:3 v/v chloroform and acetone. Collection and concentration of appropriate fractions provided the titled compound as white powder.

^{1}H NMR δ DMSO-d6 7.49 (1H, s), 7.48 (2H, d, J = 9.0 Hz), 6.93 (2H, d, J = 9.0 Hz), 6.85 (1H, s).

Step 2: 4-(4-Bromophenyloxy)-1-trityl-1H-imidazole

To a cold (0°C) solution of 4-(4-bromophenyloxy) imidazole (1.2 g, 5.0 mmol) and triethylamine (0.76 mL, 5.5 mmol) in DMF (5 mL) under an atmosphere of argon, solid trityl chloride (1.46 g, 5.3 mmol) was added. The resultant mixture was stirred at room temp overnight. The product mixture was concentrated onto silica gel, loaded onto a column of silica gel, and eluted with a mixture of 9:1 chloroform and acetone. Collection and concentration of appropriate fractions provided the titled compound as white powder.

Step 3: 4-[5-(4-Bromophenoxy)imidazol-1-ylmethyl]-1-(6-chloro-pyrazin-2-yl)-1H-pyridin-2-one

A mixture of 4-(4-bromophenyloxy)-1-trityl-1H-imidazole (0.164 g, 0.34 mmol) and 4-bromomethyl-1-(6-chloro-pyrazin-2-yl)-1H-pyridin-2-one from example 7 (98.5 mg, 0.34 mmol) in anhydrous acetonitrile (10 mL) was heated under reflux at 60 °C for 24 h. The resultant solution was concentrated, and the residue dissolved in a

mixture of methanol (10 mL) and 1,2-dichloroethane (1 mL). The solution was heated under reflux for 2 h, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 1:1 v/v 6% methanol in chloroform and chloroform saturated with ammonia gas. Collection and concentration of appropriate fractions provided the titled compound.
^{1}H NMR $CDCl_3$ δ 9.33 (1H, s), 8.60 (1H, s), 7.87 (1H, d, J = 7.6 Hz), 7.41 (1H, d, J = 8.8 Hz), 7.40 (1H, s), 6.92 (1H, d, J = 8.8 Hz), 6.67 (1H, s), 6.31 (1H, br s), 6.09 (1H, dd, J = 7.6, 1.9 Hz), 4.85 (2H, s).

Step 4: 4-[5-(4-Bromophenoxy)imidazol-1-ylmethyl]-1-(6-cyano-pyrazin-2-yl)-1H-pyridin-2-one

A mixture of 4-[5-(4-Bromophenoxy)imidazol-1-ylmethyl]-1-(6-chloropyrazin-2-yl)-1H-pyridin-2-one (79 mg, 0.17 mmol) and zinc cyanide (12 mg, 0.1 mmol) in DMF (1 mL) was purged with argon for 5 min. A solution of tetrakis(triphenylphosphine)palladium(0) (20 mg, 17 μmol) in DMF (0.5 mL) was added. The resultant mixture was stirred under argon at 80 °C overnight, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 1:1 v/v 5% methanol in chloroform and chloroform saturated with ammonia gas. Collection, concentration of appropriate fractions, and trituration of the residue with anhydrous ether provided the titled compound as white solid.
^{1}H NMR $CDCl_3$ δ 9.64 (1H, s), 8.89 (1H, s), 7.88 (1H, d, J = 7.6 Hz), 7.41 (1H, d, J = 9.1 Hz), 7.40 (1H, s), 6.92 (1H, d, J = 9.1 Hz), 6.69 (1H, s), 6.32 (1H, br s), 6.13 (1H, dd, J = 7.6, 2.0 Hz), 4.86 (2H, s).
FAB MS M+1 = 449/451 1:1.

EXAMPLE 22

4-{5-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-imidazol-1-ylmethyl}-2-methoxy-benzonitrile

Step 1: 4-(tert-butyl-dimethyl-silanyloxymethyl)-1-(3-chlorophenyl)-1H-pyridin-2-one

4-(Tert-butyldimethylsilyloxymethyl)-1H-pyridin-2-one (3.5g, 14.6 mmol) (prepared as described in *Japan Patent 6-80635 22-March(1994)* was dissolved in 3-chloroiodobenzene (25g, 105 mmol) and treated with copper (933mg, 14.6 mmol) and K_2CO_3 (2.02g, 14.6 mmol). The brown slurry was heated to 200°C for 7 hrs. The reaction mixture was triturated with EtOAc (75ml) and filtered. The filtrate was concentrated in vacuo and the residue chromatographed (silica gel, EtOAc: hexane 30:70) to afford the title compound.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.38(m, 3H), 7.30(m, 1H), 7.26 (d, J=5.3Hz, 1H), 6.65 (s, 1H), 6.19 (d, J=7.1Hz, 1H), 4.59 (s, 2H), 0.97 (s, 9H), 0.14 (s, 6H) ppm.

Step 2: 4-Hydroxymethyl-1-(3-chlorophenyl)-1H-pyridin-2-one

To a solution of 4-(tert-butyl-dimethyl-silanyloxymethyl)-1-(3-chlorophenyl)-1H-pyridin-2-one (5.11g, 14.6 mmol) in acetonitrile (75ml) in a teflon beaker was added hydrogen fluoride-pyridine (2.5ml, 87.5 mmol) and stirred for 3 hours. The reaction mixture was neutrallized with solid and aqueous sodium dicarbonate and then the solvent evaporated in vacuo. The resulting solid residue was extracted with EtOAc, dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. This residue was chromatographed (silica gel, 80-100% EtOAc:hexane gradient elution) to afford the title compound.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.38 (m, 3H), 7.30-7.25 (m, 2H), 6.66 (s, 1H); 6.24 (d, J=7.1Hz, 1H), 4.58 (d, J=6.0Hz, 2H), 2.43 (t, J=6.0Hz, 1H) ppm.

Step 3: 1-(3-chloro-phenyl)-2-oxo-1,2-dihydro-pyridine-4-carbaldehyde

To a solution of 4-hydroxymethyl-1-(3-chlorophenyl)-1H-pyridin-2-one (2.39g, 10.14 mmol) in CH_2Cl_2 (250ml) was added MnO_2 (4.41g, 50.71 mmol) and stirred for 18 hours. The suspension was filtered through celite and the pad washed with additional CH_2Cl_2 (200ml). The combined filtrates were evaporated in vacuo and chromatographed (silica gel, 5-20% EtOAc: CH_2Cl_2 gradient elution) to afford the title compound.
^1H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.47-7.41 (m, 4H), 7.30 (m, 1H), 7.10 (d, J=1.6Hz, 1H), 6.67 (dd, J=7.1 and 1.6 Hz, 1H) ppm.

Step 4: 1-(3-chloro-phenyl)-4-[hydroxy-(1-trityl-1H-imidazol-4-yl)-methyl]-1H-pyridin-2-one

To a solution of trityl-4-iodoimidazole (3.51g, 8.04 mmol) in CH_2Cl_2 (50 ml) at room temperature was added a solution of ethyl-magnesium bromide (2.81 ml of a 3M solution in diethylether, 8.43 mmol) and the mixture stirred for 2 hr. The aldehyde from step 3 (1.79g, 7.66 mmol) in CH_2Cl_2 (50ml) was added and the reaction was stirred a furthur 18 hrs at room temperature. Saturated NH_4Cl solution (200 ml) was added and the reaction stirred until the solids had dissolved. This mixture was extracted with CH_2Cl_2 (2x250ml). The combined extracts were washed with brine, dried (MgSO4) and evaporated in vacuo. The residue was chromatographed (silica gel, 5:95 MeOH: CH_2Cl_2) to afford the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44(2, 1H), 7.42-7.31(m, 10H), 7.30-7.21(m, 4H), 7.15-7.09(m, 6H), 6.78(s, 1H), 6.67(s, 1H), 6.37(dd, J=7.1 and 1.8Hz, 1H), 5.56(d, J=5.2Hz, 1H), and 4.60(d, J=5.2Hz, 1H) ppm.

Step 5: Thiocarbonic acid O-[[1-(3-chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-yl]-(1-trityl-1H-imidazol-4-yl)-methyl] ester O-phenyl ester

To a solution of the alcohol from Step 4 (2.67g, 5.02 mmol) in CH_2Cl_2 (50ml) at 0°C was added DMAP (1.34, 11.0 mmol) and phenylthiochloroformate (694µl, 5.522 mmol) and the mixture was stirred at room temperature for 18hrs. The pH of the solution was adjusted to 8.5 with sat $NaHCO_3$ solution and the aqueous extracted with CH_2Cl_2(2x200ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed (silica gel, MeOH: CH_2Cl_2 2:98 to 3:97 gradient elution) to afford the title compound.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45(s, 1H), 7.44-7.30(m, 13H), 7.30-7.19(m, 5H), 7.17-7.08(m, 7H), 6.84(s, 1H), 6.75(s, 1H), 6.50(d, J=8Hz, 1H) and 5.55(s, 1H) ppm.

Step 6: 1-(3-Chloro-phenyl)-4-(1-trityl-1H-imidazol-4-ylmethyl)-1H-pyridin-2-one

To a solution of the thiocarbonate from Step 5 (0.95, 1.4mmol) in benzene (40ml) at room temperature was added tributyl tin hydride (1.13ml, 4.19 mmol) and AIBN (46mg, 0.28 mmol). The mixture was degassed by bubbling argon through for 15 min and the mixture was heated at 85°C for 18 hrs while distilling off most of solvent. The residue was chromatographed (silica gel, MeOH: CH_2Cl_2 2:98 to 4:96 gradient elution) to afford the title compound.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.22(m, 16H), 7.19-7.07(m, 9H), 6.68(s, 1H), 6.45(s, 1H), 6.21(d, J=7.0Hz, 1H) and 3.74(2, 2H) ppm.

Step 7: 4-{5-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-imidazol-1-ylmethyl}-2-methoxy-benzonitrile

To a solution of 1-(3-Chloro-phenyl)-4-(1-trityl-1H-imidazol-4-ylmethyl)-1H-pyridin-2-one (272 mg, 0.527 mmol) from step 6 and 4-hydroxymethyl-2-methoxy-benzonitrile (90.3 mg, 0.55 mmol) in CH_2Cl_2 cooled to -78C over dry ice/acetone bath was added N,N-diisopropylethylamine (192µl, 1.1mmol) and trifluoromethanesulfonic anhydride(93µl, 0.55mmol). The reaction was allowed to slowly warm to room remperature and stirred overnight. The reaction

was diluted with methanol (10 mL), heated to reflux for 2 h, cooled and the solvent evaporated in vacuo. The residue was partitioned between sat. Na_2CO_3 (20ml) and CH_2Cl_2(2x50ml). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed (silica gel, MeOH: CH_2Cl_2 3:97 to 4:96 to 10:90 gradient elution) to afford the free base which was converted to the hydrochloride salt to afford the title compound as an off white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 9.19(s, 1H), 7.68(s, 1H), 7.56(d, J=8Hz, 1H), 7.54-7.49(m, 2H), 7.47-7.38(m, 2H), 7.28(dt, J=7.0 and 2Hz, 1H), 7.01(s, 1H), 6.83(d, J=8Hz, 1H), 6.18(dd, J=7 and 2Hz, 1H), 6.05(s, 1H), 5.57(2, 2H), 4.07(s, 2H) and 3.91(s, 3H) ppm.

Elemental Analysis cald $C_{24}H_{19}ClN_4O_2$ HCl 0.2 C_4H_8O 0.95 H_2O:
C, 59.33; H, 4.72; N, 11.16.
Found: C, 59.06; H, 7.06; N, 10.85.

HRMS(M^+) cald: 431.1269
Found: 431.1271

EXAMPLE 23

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber et al., J. Biol. Chem. 265:14701-14704 (1990), Pompliano, et al., Biochemistry 31:3800 (1992) and Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 µl containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [^{3}H]-farnesyl diphosphate ([^{3}H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 µg/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvestor, washed with 100% ethanol, dried and counted in an LKB

β-plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^{3}H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μM $ZnCl_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 μl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compounds of the instant invention described in the above Examples 1-22 were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC_{50} of <50 μM.

EXAMPLE 24

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemeted with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[^{35}S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM $MgCl_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml

antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 25

In vivo growth inhibition assay

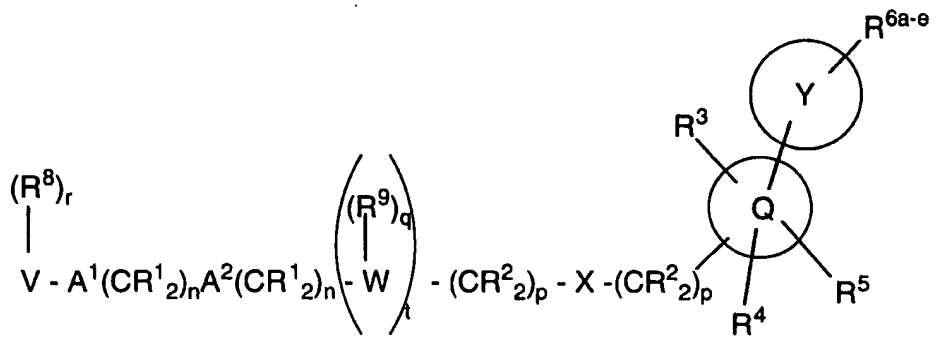
To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-*ras*, v-*raf*, or v-*mos* oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1 x 10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the

concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

WHAT IS CLAIMED IS:

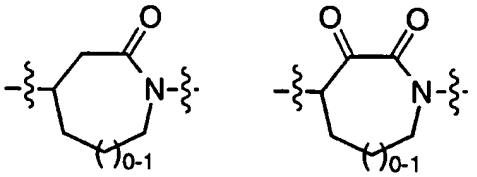
1. A compound which inhibits farnesyl-protein transferase of the formula A:

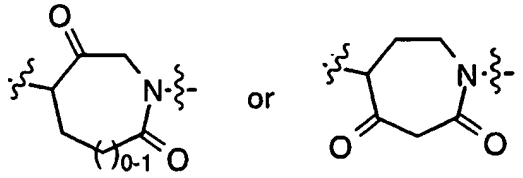


A

wherein:

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not





Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

R^1 and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

$R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

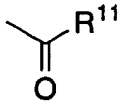
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^7 is selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c)  ,

d) $-SO_2R^{11}$,

e) $N(R^{10})_2$ or

f) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is independently selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)2-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

R^{13} is selected from hydrogen, C_1-C_6 alkyl, cyano, C_1-C_6 alkylsulfonyl and C_1-C_6 acyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)2N(R^{10})-, -N(R^{10})S(O)2-, or $S(O)_m$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

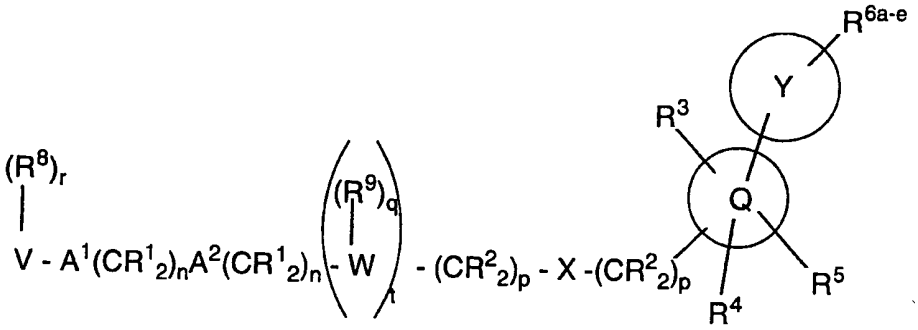
W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR^7-, -NR^{7}C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{7}C(O)-, -NR^7-, -S(O)2N(R^{10})-, -N(R^{10})S(O)2- or -S(=O)m-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is independently 0, 1, 2, 3 or 4;
q is 0, 1, 2 or 3;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
t is 0 or 1;

or a pharmaceutically acceptable salt thereof.

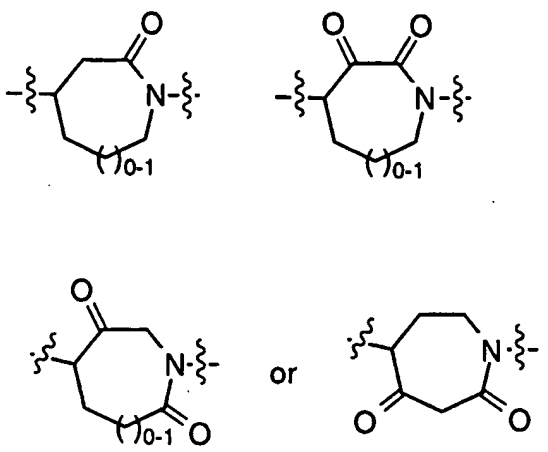
2. The compound according to Claim 1, which inhibits farnesyl-protein transferase, of the formula A:



A

wherein:

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not



Y is selected from: phenyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thiazolyl, isothiazolyl, tetrahydrofuryl, piperdinyl, thiazolidinyl, piperazinyl and tetrahydrothienyl;

R^1 is independently selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl;

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl;

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

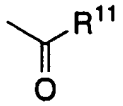
any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-,

-CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^7 is selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c)  ,

d) $-SO_2R^{11}$,

e) $N(R^{10})_2$ or

f) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)2-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

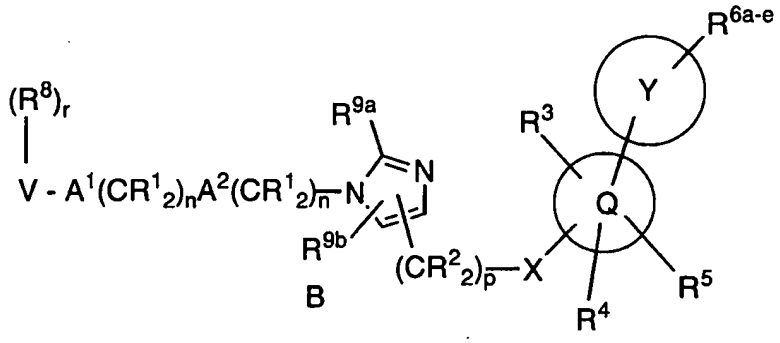
W is a heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, triazolyl or isoquinolinyl;

X is a bond, O, -C(=O)-, -CH=CH-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7-$, $-S(O)_2N(R^{10})-$, $-N(R^{10})S(O)_2-$ or $-S(=O)_m-$;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is independently 0, 1, 2, 3 or 4;
q is 0, 1, 2 or 3;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
t is 0 or 1;

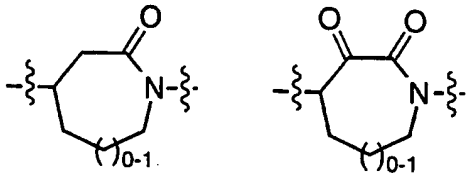
or a pharmaceutically acceptable salt thereof.

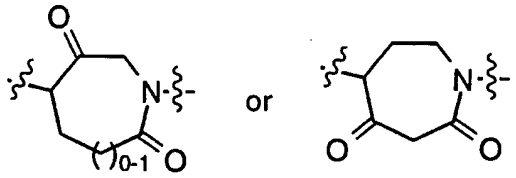
3. The compound according to Claim 1, which inhibits farnesyl-protein transferase, of the formula B:



wherein:

Q is a 5 or 6 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not





Y is selected from: phenyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thiazolyl, isothiazolyl, tetrahydrofuryl, piperdinyl, thiazolidinyl, piperazinyl and tetrahydrothiophenyl;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $(R^{10})_2NS(O)_2$-, $R^{11}S(O)_mNR^{10}$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl and halogen;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, $(C_1$-C_6 alkyl$)_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

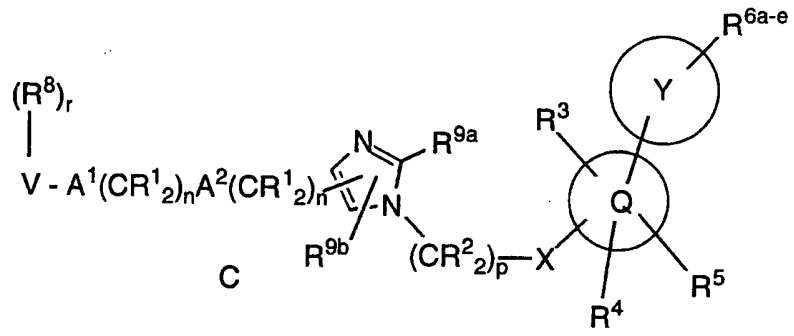
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

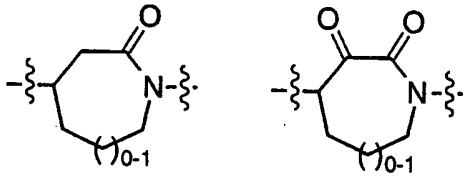
or a pharmaceutically acceptable salt thereof.

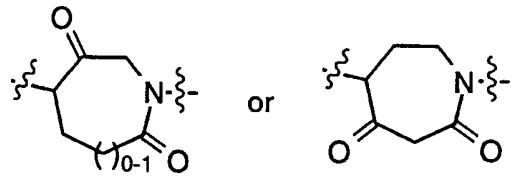
4. The compound according to Claim 1, which inhibits farnesyl-protein transferase, of the formula C:



wherein:

Q is a 5 or 6 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not





Y is selected from: phenyl, thiophenyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thiazolyl, isothiazolyl, tetrahydrofuryl, piperdinyl, thiazolidinyl, piperazinyl and tetrahydrothiophenyl;

R1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-,

$R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-C(NR^{10})-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-C(NR^{10})-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl and halogen;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-

C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)$_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)$_m$;

V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

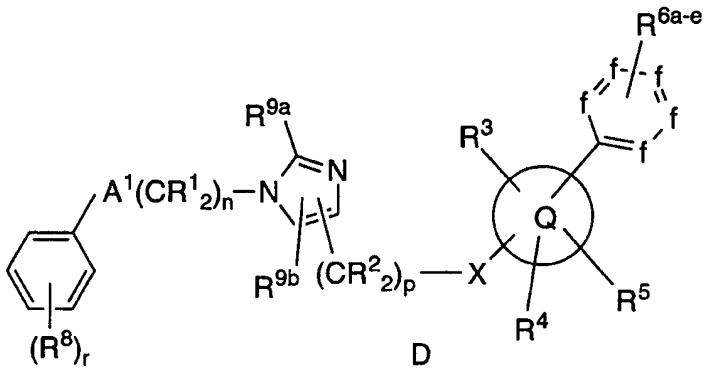
X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond or O;
and
r is 0 to 5, provided that r is 0 when V is hydrogen;

or a pharmaceutically acceptable salt thereof.

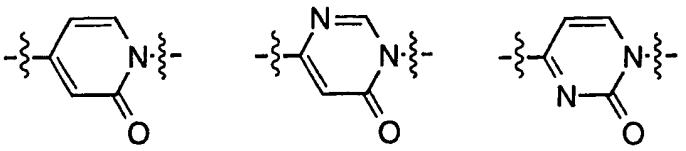
5. The compound according to Claim 3, which inhibits farnesyl-protein transferase, of the formula D:

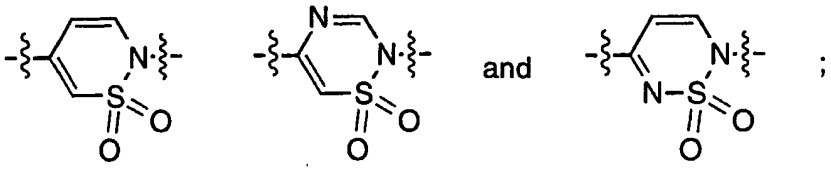


D

wherein:

Q is selected from





from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)2-amino-C_1-C_6 alkyl,

acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

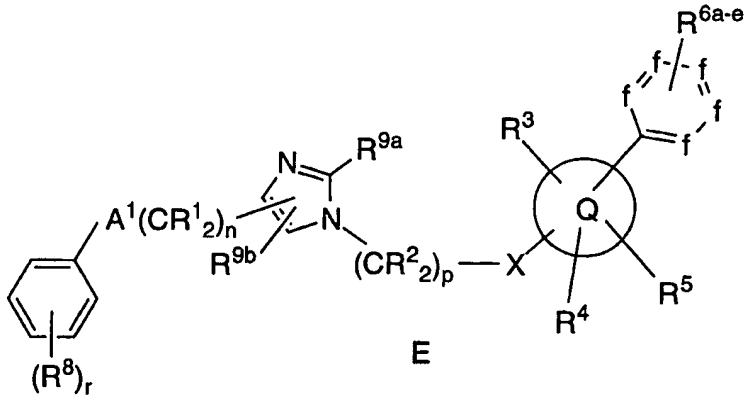
A^1 is selected from: a bond, -C(O)-, O, -N(R^{10})-, or $S(O)_m$;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-,

n is 0 or 1; provided that n is not 0 if A^1 is a bond, O, -N(R^{10})- or $S(O)_m$;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4; and
r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

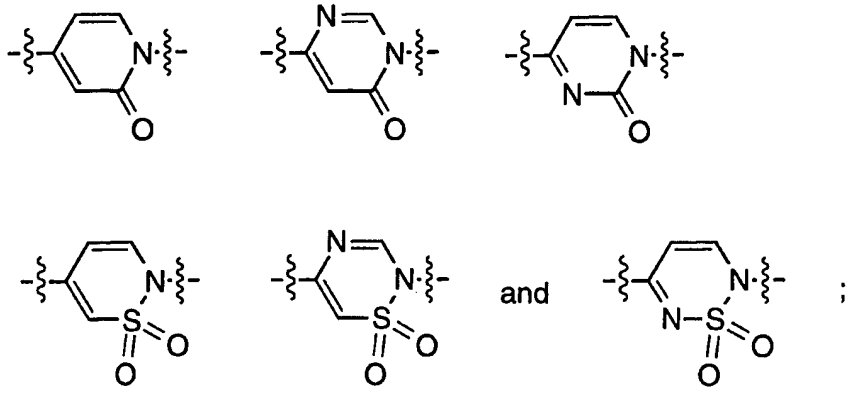
6. The compound according to Claim 4, which inhibits farnesyl-protein transferase, of the formula E:



E

wherein:

Q is selected from



from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, $(C_1$-C_6 alkyl$)_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^{10})-, or $S(O)_m$;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-,

n is 0 or 1; provided that n is not 0 if A^1 is a bond, O, -N(R^{10})- or $S(O)_m$;

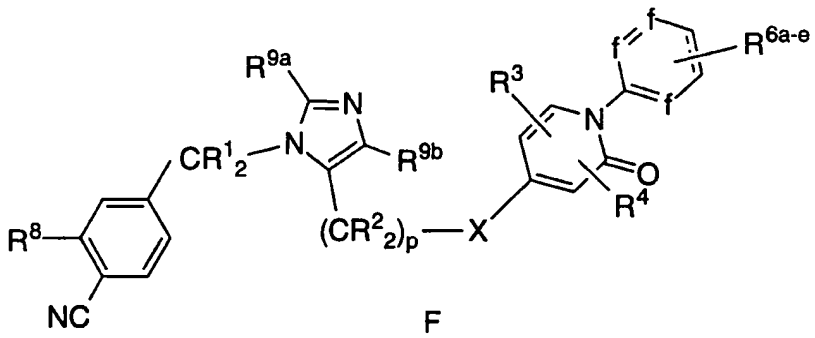
m is 0, 1 or 2;

p is 0, 1, 2, 3 or 4; and

r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

7. The compound according to Claim 5, which inhibits farnesyl-protein transferase, of the formula F:



F

wherein:

from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or F,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, CH_3 and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)4$- and -$(CH_2)3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, $(C_1$-C_6 alkyl$)_2$-amino-C_1-C_6 alkyl,

acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

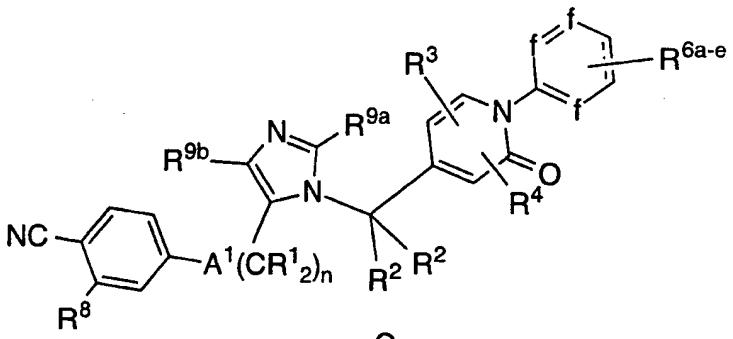
R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 6, which inhibits farnesyl-protein transferase, of the formula G:



G

wherein:

from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$, F or C_1-C_6 alkyl;

R^2 is independently selected from:

a) hydrogen,

b) aryl, heterocycle or C_3-C_{10} cycloalkyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, CH_3 and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)2-amino-C_1-C_6 alkyl,

acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heteraryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^{10})-, or $S(O)_m$;

m is 0, 1 or 2; and
n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

9. A compound which inhibits farnesyl-protein transferase which is selected from:

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-[3-(2-Oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(6'-Methyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}-2-methoxy-benzonitrile

4-[3-(2-Oxo-1-pyrimidin-2-yl-1,2-dihydro-pyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-{3-[1-(6-chloro-pyrazin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile

4-[3-(3'-Methyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(6'-chloro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(6-'Triflouromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-{3-[1-(6-Chloro-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile

4-{3-[1-(6-Chloro-pyrazin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-2-methoxy-benzonitrile

4-{3-[1-(6-Chloro-4-methyl-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile

3-[3-(6'-chloro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(5'-Cyano-2-oxo-2H-[1,3']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(4'-Trifluoromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(6'-Methoxy-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(3'-Nitro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-[3-(3'-Trifluoromethyl-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile

4-{3-[1-(6-Trifluromethyl-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-yl methyl]-3H-imidazol-4-ylmethyl}-benzonitrile

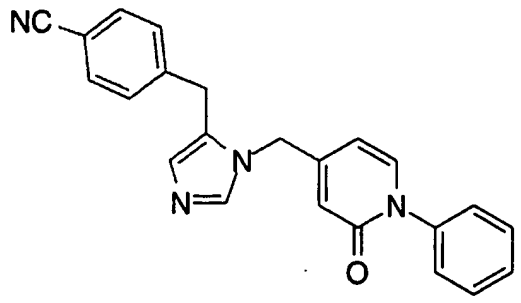
4-[5-(4-Bromophenoxy)imidazol-1-ylmethyl]-1-(6-cyanopyrazin-2-yl)-1H-pyridin-2-one

4-{5-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-imidazol-1-ylmethyl}-2-methoxy-benzonitrile

or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 9 which is:

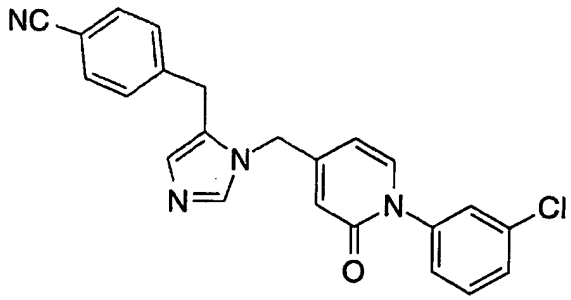
4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile



or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 9 which is:

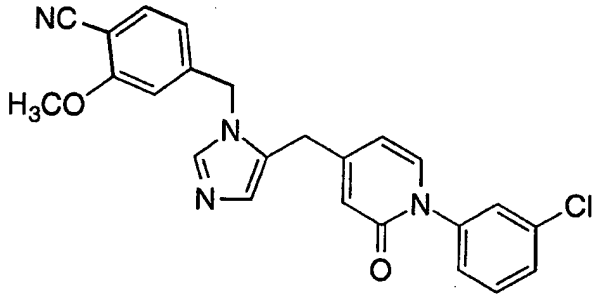
4-{3-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydropyridin-4-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile



or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 9 which is:

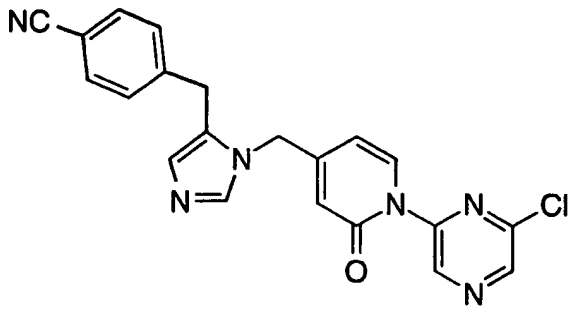
4-{5-[1-(3-Chloro-phenyl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-imidazol-1-ylmethyl}-2-methoxy-benzonitrile



or a pharmaceutically acceptable salt thereof.

13. The compound according to Claim 9 which is:

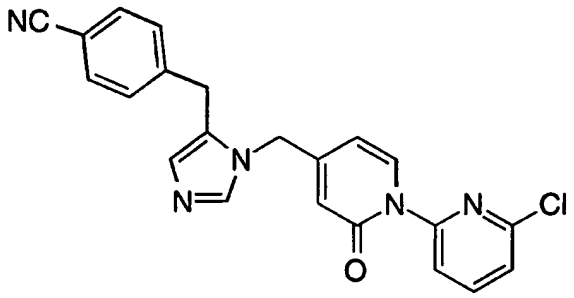
4-{3-[1-(6-Chloro-pyrimidin-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylmethyl]-3H-imidazol-4ylmethyl}-benzonitrile



or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 9 which is:

3-[3-(6'-chloro-2-oxo-2H-[1,2']bipyridinyl-4-ylmethyl)-3H-imidazol-4-ylmethyl]-benzonitrile



or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

16. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

17. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 4.

18. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 9.

19. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

20. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 16.

21. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 17.

22. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

23. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

24. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 16.

25. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 17.

26. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 18.

27. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

28. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

29. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

30. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

31. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 15.

32. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

33. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/23888

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A01N 43/40, 54, 58; C07D 401/00
US CL :514/252, 256, 333, 341; 544/333, 405; 546/256, 272.7
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/252, 256, 333, 341; 544/333, 405; 546/256, 272.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, REGISTRY

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database CAPLUS on STN, DN:126:31349, PAYNE et al, 'Use of Pyrazolylpiperidine Derivatives as Alpha 1a Adrenergic Receptor Antagonists, for Treatment of Benign Prostatic Hypertrophy'. Abstract, WO 9632938 A1, especially 1-(2-furanylmethyl)-4-(4-methyl-5-phenyl-1H-pyrazol-3-yl)piperidine.	1, 15, 32, 33
X	US 4,074,051 A (STEVENS) 14 February 1978, especially Examples 11, 12, 14-16 and 19.	1, 15, 32, 33
X	US 4,287,195 A (HEERES et al.) 01 September 1981, especially the compounds of the table beginning in column 17. and ending in column 20.	1, 15, 32, 33

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
25 APRIL 1998	11 JUN 1998

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	GARTH M. DAHLEN
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/23888

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database CAPLUS on STN, DN:114:62092, AONO et al, 'Preparation of Pyrazolones and Peroxylipid Formation Inhibitors and Collagenase Inhibitors Containing Them'. Abstract, JP 02229169 A2, especially RN 131647-55-7.	1, 2, 15, 19, 23, 32, 33
X	US 4,329,470 A (GRISAR et al.) 11 May 1982, especially claim 1.	1, 2, 15, 32, 33
X	US 4,826,835 A (KUHLA et al.) 02 May 1989, especially the compounds having R=methylpiperidino, methylmorpholino, or methylpiperazine, see Tables I-IV.	1, 15, 32, 33
X	US 4,914,207 A (NAGEL et al.) 03 April 1990, especially the table of columns 7-12.	1-4, 15-17, 32 and 33
X	US 5,478,934 A (YUAN et al.) 26 December 1995, especially Examples I-III.	1-4, 15-17, 32, 33
X	US 5,441,970 A (REITZ et al.) 15 August 1995, especially Examples 1-6, 10-20, 25, 26, 31-43.	1, 2, 15, 32, 33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/23888

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-26 and 32-33 in part

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/23888

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

The following table defines the inventions claimed in this application. By selecting a single radical from each of the following variables (as defined in Formula A): W, $-(CR_2^2)_p-X-(CR_2^2)_p-$, Q, and Y and a single method of use, one can arrive at 168 groups.

Variables of Formula A

W - a^1) heterocycle,
b^1) absent;

$-(CR_2^2)_p-X-(CR_2^2)_p-$ - a^2) $-CH_2-$,
b^2) -O-;

Q - a^3) 4-7 membered ring with 1-3 nitrogens,
b^3) 4-7 membered ring with nitrogen and/or sulfur and/or oxygen;

Y - a^4) 5-7 membered carbocyclic ring,
b^4) 5-7 membered ring with nitrogen as the only heteroatom,
c^4) 5-7 membered ring with nitrogen and/or sulfur and/or oxygen:

Method of Treating Diseases Groups

I) cancer,
II) neurofibromin benign proliferative disorder,
III) blindness related to retinal vascularization,
IV) hepatitus delta and related viral infections,
V) restenosis,
VI) polycystic kidney disease,
VII) antifungal.

The variables as defined supra combine to form 168 groups. For complete coverage of the claimed subject matter, a separate compound group and a separate method group encompassing the instantly claimed compounds and methods not represented by the 168 groups are included resulting in a total of 170 groups. Please note, the elected method group(s), composition (claim 32) and process (claim 33) will be examined to the extent each reads on the elected compound group(s).

A sample selection of an individual group is as follows:
Group I, claims 10-12 and 1-9, 15-26 in part, drawn to compounds, compositions and methods of use wherein the compound is of Formula A, wherein W = heterocycle; $-(CR_2^2)_p-X-(CR_2^2)_p-$ = $-CH_2-$; Q = 4-7 membered ring with 1-3 nitrogens; Y = carbocycle; method of treating cancer.

In a communication faxed April 24, 1998, Applicant's Attorney, Mr. David Muthard paid for 2 additional groups. Accordingly a search will be performed for a compound of Formula A wherein W = heterocycle; $-(CR_2^2)_p-X-(CR_2^2)_p-$ = $-CH_2-$; Q = 4-7 membered ring with 1-3 nitrogens; Y = carbocycle, a 5-7 membered ring with nitrogen as the only heteroatom, and a 5-7 membered ring with nitrogen and/or sulfur and/or oxygen; method of treating cancer.

The inventions listed as Groups 1-170 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: there is NO SIGNIFICANT STRUCTURAL ELEMENT shared by all of the alternatives just a string of variables. In accordance with Rule 13.2, Compound 11 of FURUKAWA et al US 4,340,598 is an example that at least one Markush alternative is not novel over the prior art; therefore, the finding that the instantly claimed genus of compounds lacks unity is appropriate. Regarding the multiple methods, each malady has been placed in a separate grouping since they have different etiologies, ie. a compound that is found to be useful in the treatment of cancer would not apriori be useful in the treatment of restenosis.